

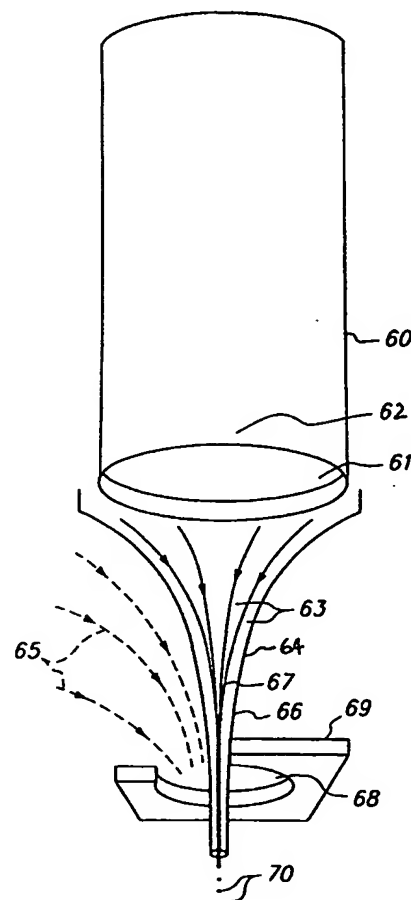
## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>B05B 7/06, A61M 15/00</b>		A1	(11) International Publication Number: <b>WO 99/30834</b>
			(43) International Publication Date: 24 June 1999 (24.06.99)
(21) International Application Number: <b>PCT/IB98/02055</b>		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 16 December 1998 (16.12.98)			
(30) Priority Data: P 9702654 17 December 1997 (17.12.97) ES 09/191,592 13 November 1998 (13.11.98) US			
(71) Applicant (for all designated States except US): UNIVERSIDAD DE SEVILLA [ES/ES]; Vicerrectorado de Investigación, Valparaíso, 5, 2ª planta, E-41013 Sevilla (ES).			
(72) Inventor; and			
(75) Inventor/Applicant (for US only): GANAN CALVO, Alfonso [ES/ES]; Camilo Jose Cela, nº 4, Bloque 8, 3ªA, E-41018 Sevilla (ES).			
(74) Agent: UNGRIA LOPEZ, Javier; Avenida Ramon y Cajal, 78, E-28043 Madrid (ES).			
		<b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	

(54) Title: DEVICE AND METHOD FOR CREATING AEROSOLS FOR DRUG DELIVERY

## (57) Abstract

A drug delivery device and method is disclosed which produces aerosolized particles of pharmaceutically active drug for delivery to a patient by inhalation. The device is comprised of a liquid feeding source such as a channel to which formulation is added at one end and expelled through an exit opening. The feeding channel is surrounded by a pressurized chamber into which gas is fed and out of which gas is expelled from an opening. The opening from which the gas is expelled is positioned directly in front of the flow path of liquid expelled from the feeding channel. Various parameters are adjusted so that pressurized gas surrounds liquid flowing out of the feeding channel in a manner so as to maintain a stable capillary microjet of liquid until the liquid exits the pressure chamber opening and is aerosolized. The aerosolized particles having a uniform diameter in the range of about 1 to 5 microns are inhaled into a patient's lungs and thereafter reach the patient's circulatory system.



**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon			PT	Portugal		
CN	China	KR	Republic of Korea	RO	Romania		
CU	Cuba	KZ	Kazakstan	RU	Russian Federation		
CZ	Czech Republic	LC	Saint Lucia	SD	Sudan		
DE	Germany	LI	Liechtenstein	SE	Sweden		
DK	Denmark	LK	Sri Lanka	SG	Singapore		
EE	Estonia	LR	Liberia				

## DEVICE AND METHOD FOR CREATING AEROSOLS FOR DRUG DELIVERY

### FIELD OF THE INVENTION

5           This invention relates generally to the field of aerosols and more particularly to devices and methods for creating aerosols of pharmaceutical formulations for delivery to a human patient, preferably by inhalation.

### BACKGROUND OF THE INVENTION

10           Aerosolizing formulations for inhalation has been considered as a convenient alternative to injection for decades. This alternative to injections is particularly interesting for drugs which cannot be delivered orally, e.g. insulin. Although most compounds will effectively move from the lungs into the circulatory system there is considerable unpredictability in how much aerosolized formulation reaches the areas of the lungs where  
15 the material can move into the circulatory system. This results in inefficiency and unpredictability of dosing. A number of devices have been proposed for improving the efficiency of aerosol delivery, monitoring patients and teaching patients to correctly use delivery devices.

          There are several different types of devices which use generally different  
20 mechanisms and methodologies to produce aerosols for inhalation. The most commonly used device is a metered dose inhaler (MDI) which comprises a drug formulation container with the formulation including a low boiling point propellant. The formulation is held in the container under pressure and a metered dose of formulation is released as an aerosol when the valve on the container is opened. The low boiling point propellant quickly  
25 evaporates or "flashes" when the formulation is exposed to atmospheric pressure outside the container. The particles of formulation containing the drug without the propellant are inhaled into the patient's lungs and thereafter migrate into the patient's circulatory system. There are a number of different types of MDI devices. Devices of this type are disclosed in U.S. Patents 5,404,871 issued April 11, 1995 and 5,364,838 issued November 15,  
30 1994.

          Another type of device is the dry powder inhaler (DPI) device. As indicated by the name such devices use formulations of dry powder which powder is blown into an

aerosolized cloud via a burst of gas. Typical DPI devices are shown in U.S. Patents 5,775,320 issued July 7, 1998 and 5,740,794 issued April 21, 1998.

Yet another type of aerosol delivery device forces a formulation through a porous membrane. Formulation moving through the pores breaks up to form small particles which are inhaled by the patient. Devices of this type are shown in U.S. Patents 5,554,646 issued August 13, 1996 and 5,522,385 issued June 4, 1996.

Each of these devices has some advantages and disadvantages. The object of each is substantially the same - to repeatedly produce a fine mist aerosol wherein the particles are substantially uniform in size and within a size range of about 1 micron to about 5 microns. A patient can be accurately dosed if the device can repeatedly start with a given amount of formula and produce a known amount of aerosol with particles having sizes within a known range. The present invention endeavors to provide a device and method for obtaining accurate repeatable dosing of a patient with an aerosol.

## SUMMARY OF THE INVENTION

Aerosolized particles within a desired size range (e.g., 1 micron to about 5 microns) are produced from a liquid formulation comprised of a pharmaceutical active drug and a carrier. The particles produced all have substantially the same particle diameter  $\pm 3\%$  to  $\pm 30\%$ , e.g. all particles in the aerosol have a diameter of 2 microns  $\pm 3\%$  to  $\pm 10\%$ . The formulation is provided in any desired manner (e.g., forced through a channel of a feeding needle and expelled out of an exit opening of the needle). Simultaneously, gas contained in a pressure chamber (which surrounds at least the area where the formulation is provided, e.g., surrounds the exit opening of the needle) is forced out of an opening positioned in front of the formulation, e.g., directly in front of the flow path of the formulation being expelled from the feeding needle. Various parameters are adjusted to obtain a super critical flow of liquid characterized by a stable liquid-gas interface and a stable capillary jet of the liquid which forms particles on exiting the opening of the pressurized chamber which particles will all (90% or more) have substantially the same diameter, i.e., a monodisperse aerosol.

An object of the invention is to provide a device for aerosolized delivery of a pharmaceutically active drug formulation or a diagnostic formulation.

Another object is to provide a method of creating an aerosol of consistent particle size ( $\pm 3$  to 30% or preferably  $\pm 3$  to 10% difference in diameter) which aerosol is inhalable by a patient for aerosolized delivery of drugs or diagnostics.

5 A feature of the invention is that the diameter of the opening from which liquid is expelled, the diameter of the opening from which gas is expelled and the distance between these two openings is adjustable and is adjusted to obtain a stable liquid-gas interface which results in a stable capillary microjet being formed by the liquid expelled which microjet is focused on an exit opening by the flow of surrounding gas.

10 Another feature of the invention is that the viscosities and velocities of the fluids can be chosen with consideration to other adjusted parameters to obtain a capillary supercritical flow of liquid.

Another feature of the invention is that the liquid can be a single liquid, two or more (miscible or immiscible) liquids mixed, a solution or a suspension.

15 An advantage of the invention is that the gas flowing with the particles prevents the particles from agglomerating thereby maintaining a monodisperse aerosol.

An advantage of the invention is that it consistently produces aerosols having particles with a desired particle diameter e.g. 1 to 5 microns.

An advantage of the invention is that the device of the invention is energy efficient in terms of the energy used to create small particles for inhalation.

20 Another advantage is that the structure of the device and its use are simple.

Another advantage is that clogging of the exit opening of the pressure chamber is substantially eliminated because liquid is kept out of contact with the surface of the exit opening by a surrounding focused funnel of gas which flows out of the pressure chamber exit opening.

25 Yet another advantage is that particles produced are substantially smaller in size than would be expected based on the diameter of the exit opening of the pressure chamber due to focusing the flow of the liquid with the flow of surrounding gas.

30 An aspect of the invention is a hand-held, self-contained portable drug delivery device which consistently produces small aerosolized particles which are relatively uniform in size.

Another aspect of the invention is a device and method which produces multiple streams of aerosol thereby quickly aerosolizing a large dose of formulation for inhalation by a patient.

These and other aspects, objects, features and advantages will become apparent to those skilled in the art upon reading this disclosure in combination with the figures provided.

### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic view showing the basic components of one embodiment of the invention with a cylindrical feeding needle as a source of formulation.

Figure 2 is a schematic view of another embodiment of the invention with two concentric tubes as a source of formulation.

Figure 3 is a schematic view of yet another embodiment showing a wedge-shaped planar source of formulation. Figure 3a illustrates a cross-sectional side view of the planar feeding source and the interaction of the fluids. Figure 3b show a frontal view of the openings in the pressure chamber, with the multiple openings through which the atomizate exits the device. Figure 3c illustrates the channels that are optionally formed within the planar feeding member. The channels are aligned with the openings in the pressure chamber.

Figure 4 is a schematic view of a stable capillary microjet being formed and flowing through an exit opening to thereafter form a monodisperse aerosol.

Figure 5 is a graph of data where 350 measured values of  $d_j/d_o$  versus  $Q/Q_o$  are plotted.

Figure 6 is a schematic view of the critical area of a device of the type shown in Figure 1 showing gas surrounded by liquid expelled into a liquid to form bubbles.

Figure 7 is a schematic view as in Figure 6 but with the bubbles flowing into a gas.

Figure 8 is a schematic view as in Figure 6 but with two immiscible liquids flowing into a gas.

## DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Before the present aerosol device and method are described, it is to be understood that this invention is not limited to the particular components and steps described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a", "and," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a particle" includes a plurality of particles and reference to "a fluid" includes reference to a mixture of fluids, and equivalents thereof known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

25

## DEFINITIONS

The term "formulation" is used to describe any single liquid, mixture, solution, suspension or the like which is a flowable liquid at room temperature and comprises either a pharmaceutically active compound, a diagnostic compound or a compound which becomes an active compound after entering a patient, e.g. prodrugs or DNA encoding proteins. The formulation is preferably further comprised of a carrier and more preferably is a liquid that has physical properties (e.g., viscosity) such that when the formulation is moved through a device of the invention the formulation is aerosolized into particles (0.1

to 10 microns in diameter) which are inhaled into the lungs of a patient and preferably reach the circulatory system. The carrier may be any pharmaceutically acceptable material and is preferably a flowable liquid which is compatible with the active agent.

Formulations are preferably solutions, e.g., aqueous solutions, ethanolic solutions, aqueous/ethanolic solutions, saline solutions, colloidal suspensions and microcrystalline suspensions. Formulations can be solutions or suspensions of drugs (including systemically active drugs, e.g. insulin, insulin analogs including monomeric insulin such as insulin lispro) in the above mentioned liquids.

The term "carrier" shall mean a substantially inactive (biologically) component of a formulation such as a pharmaceutically acceptable excipient material which an active ingredient such as a drug, a diagnostic agent, prodrug or a gene vector is mixed with, suspended or dissolved in. The carrier is preferably a flowable liquid. Useful carriers do not adversely interact with the drug, diagnostic or gene vector and have properties which allow for the formation of aerosolized particles preferably particles having a diameter in the range of 0.1 to 10.0 microns (more preferably 1 to 5 microns) when a formulation comprising the carrier and active ingredient is aerosolized out of a device of the invention. Carriers include water, ethanol, saline solutions and mixtures thereof with pure water being preferred. Other carriers can be used provided that they can be formulated to create a suitable aerosol and do not adversely effect the active component or human lung tissue.

The term "active compound" means a compound which is either a pharmaceutically active drug, becomes or produces a therapeutic compound in the body or is a detectably labeled compound. In turn, a "pharmaceutically active drug" or therapeutic compound shall be interpreted to mean any pharmaceutically effective compound used in the treatment of disease. A "detectably labeled compound" includes compounds which are radioactively labeled see U.S. Patent 5,829,436 issued November 3, 1998 Re: detectable labels.

Pharmaceutical formulations for use in the invention may be comprised of any therapeutic agent that can be atomized for patient delivery, e.g. for pulmonary delivery using an inhalation delivery system. Examples of such pharmaceutical compositions may be found in the Physicians Desk Reference (1998), and Remington: The Science and Practice of Pharmacy 19<sup>th</sup> Edition (1995), both of which are incorporated herein by reference. These formulations may be in any form capable of atomization, such as a solution, a suspension, an



emulsion, a slurry, etc., provided the dynamics of the form render it capable of forming a capillary microjet upon exposure to a second fluid.

The terms "electronic particle sensing device" and "electronic detection system" refer to a device or other means for measuring and counting particles present in an aerosol  
5 mist.

The term "reporting means" is used herein to indicate a means by which information obtained from a monitoring device such as an electronic particle sensing device or a device which monitors and records information relating to the patient's respiratory movement, may be provided to the user.

10 The term "aerosol bolus" is used herein to describe a volume of air greater than 50 ml and less than 4 liters which has suspended within it particles of a formulation wherein the particles have a diameter in the range of 0.1 to 10 microns, preferably 1 to 5 microns, and preferably the total volume of formulation is from 5  $\mu$ l to 10,000  $\mu$ l. About 10  $\mu$ l of particles having a diameter of about 1 to 3 microns are present in a volume of  
15 about 50 ml to 2 liters, preferably 100 ml to 1,000 ml.

The term "aerosol" means any part of an aerosol bolus as described above.

The terms "air", "particle free air", "aerosol free air," and the like, are used interchangeably herein to describe a volume of air which is substantially free of other material and, in particular, free of particles intentionally added such as particles of  
20 formulation which create the aerosol. The term means that the air does not include particles of formulation which have been intentionally added but is not intended to imply that the normal surrounding air has been filtered or treated to remove all particles although filtering can take place. Air is the preferred gas to use with drug delivery it being noted that other non-toxic gases, e.g., CO<sub>2</sub> can be used.

25 The term "measuring" describes an event whereby the (1) total lung capacity, (2) inspiratory flow rate or (3) inspiratory volume of the patient is measured and/or calculated. The information is preferably used in order to determine an optimal point in the inspiratory cycle at which to release an aerosol and/or a particle free volume of air. An actual measurement of both rate and volume may be made or the rate can be directly  
30 measured and the volume calculated based on the measured rate. The total lung capacity can be measured or calculated based on the patient's height, sex and age. It is also preferable to continue measuring inspiratory flow during and after aerosol delivery and to

record inspiratory flow rate and volume before, during and after the release of formulation. Such reading makes it possible to determine if aerosolized formulation was properly delivered to the patient.

The term "monitoring" event shall comprise determining the character of an aerosol such as the size, number and speed of the particles in the aerosol, further, monitoring may comprise measuring lung functions such as inspiratory flow, inspiratory flow rate, and/or inspiratory volume so that a patient's lung function as defined herein, can be evaluated during before and/or after delivery thereby making it possible to evaluate the effect of formulation such as respiratory drug delivery on the patient's lung function.

10 The term "inspiratory flow rate" shall mean a value of air flow rate determined, calculated or measured based on the speed of the air passing a given point in a measuring device assuming atmospheric pressure  $\pm 5\%$  and a temperature in the range of about  $10^{\circ}\text{C}$  to  $40^{\circ}\text{C}$ .

15 The term "inspiratory flow" shall be interpreted to mean a value of air flow calculated based on the speed of the air passing a given point along with the volume of the air that has passed that point with the volume calculation being based on integration of the flow rate data and assuming atmospheric pressure,  $\pm 5\%$  and temperature in the range of about  $10^{\circ}\text{C}$  to about  $40^{\circ}\text{C}$ .

20 The term "inspiratory volume" shall mean a determined, measured or calculated volume of air passing a given point into the lungs of a patient assuming atmospheric pressure  $\pm 5\%$  and a temperature in the range of  $10^{\circ}\text{C}$  to  $40^{\circ}\text{C}$ .

The terms "lung function" and "pulmonary function" are used interchangeably and shall be interpreted to mean physically measurable operations of a lung including but not limited to (1) inspiratory and (2) expiratory flow rates as well as (3) lung volume, i.e., total lung capacity. Methods of quantitatively determining pulmonary function are used to measure lung function. Quantitative determination of pulmonary function may be important when delivering any formulation and in particular respiratory drugs in order to direct the aerosol to a specific area of the lung and to determine effectiveness. Methods of measuring pulmonary function most commonly employed in clinical practice involve timed measurement of inspiratory and expiratory maneuvers to measure specific parameters. For example, forced vital capacity (FVC) measures the total volume in liters exhaled by a patient forcefully from a deep initial inspiration. This parameter, when evaluated in

conjunction with the forced expired volume in one second ( $FEV_1$ ), allows bronchoconstriction to be quantitatively evaluated. A problem with forced vital capacity determination is that the forced vital capacity maneuver (i.e. forced exhalation from maximum inspiration to maximum expiration) is largely technique dependent. In other words, a given patient may produce different FVC values during a sequence of consecutive FVC maneuvers. The FEF 25-75 or forced expiratory flow determined over the mid-portion of a forced exhalation maneuver tends to be less technique dependent than the FVC. Similarly, the  $FEV_1$  tends to be less technique dependent than FVC. In addition to measuring volumes of exhaled air as indices of pulmonary function, the flow in liters per minute measured over differing portions of the expiratory cycle can be useful in determining the status of a patient's pulmonary function. In particular, the peak expiratory flow, taken as the highest air flow rate in liters per minute during a forced maximal exhalation, is well correlated with overall pulmonary function in a patient with asthma and other respiratory diseases. The present invention carries out treatment by administering formulation in a delivery event and monitoring lung function in a monitoring event. A series of such events may be carried out and repeated over time to determine if lung (see U.S. Patent 5,404,871) function is improved.

Each of the parameters discussed above is measured during quantitative spirometry. A patient's individual performance can be compared against his personal best data, individual indices can be compared with each other for an individual patient (e.g.  $FEV_1$  divided by FVC, producing a dimensionless index useful in assessing the severity of acute asthma symptoms), or each of these indices can be compared against an expected value. Expected values for indices derived from quantitative spirometry are calculated as a function of the patient's sex, height, weight and age. For instance, standards exist for the calculation of expected indices and these are frequently reported along with the actual parameters derived for an individual patient during a monitoring event such as a quantitative spirometry test.

The terms "particles", "aerosolized particles" and "aerosolized particles of formulation" are used interchangeably herein and shall mean particles of formulation comprised of any pharmaceutically active ingredient, a compound which becomes such in the body (e.g. a prodrug or DNA encoding a protein) or a diagnostic compound. Any of these is preferably with a carrier, (e.g., a pharmaceutically active respiratory drug and

carrier). Particles of a liquid formulation are formed upon forcing the formulation from anywhere it is provided (e.g., the feeding needle) and then out of the pressure chamber exit orifice. The particles have a size which is sufficiently small such that when the particles are formed they remain suspended in the air for a sufficient amount of time such  
5 that the patient can inhale the particles into the patient's lungs. The particles have a size in the range of 0.1 micron to about 10 microns, preferably 1 to 5 microns. Particle diameter is an aerodynamic diameter.

In referring to particle diameter, the diameter measurement given is the "aerodynamic diameter" measurement which is the diameter of a sphere of unit density  
10 that has the same terminal sedimentation velocity in air under normal atmospheric conditions as the particle in question. This is pointed out in that it is difficult to accurately measure the diameter of small particles using current technology and the shape may be continually changing. Thus, the diameter of one particle of material of a given density will be said to have the same diameter as another particle of the same or a different  
15 material if the two particles have the same terminal sedimentation velocity in air under the same conditions.

### DEVICE IN GENERAL

The present disclosure focuses on the use of an aerosol creation device to  
20 produce aerosolized liquid formulations for delivery of drugs to patients - preferably by inhalation into the lungs.

The basic technology of the invention comprises (1) a means for supplying a first fluid; and (2) a pressure chamber supplied with a second fluid. The first fluid is generally a liquid and preferably aqueous. The second fluid is generally a gas and preferably air.  
25 However, the first fluid may be a gas and second fluid a liquid or both fluids may be liquid provided the first and second fluid are sufficiently different from each other (immiscible) so as to allow for the formation of a stable microjet of the first fluid moving from the supply means to an exit port of the pressure chamber. Notwithstanding these different combinations of gas-liquid, liquid-gas, and liquid-liquid the invention is generally  
30 described with a liquid formulation being expelled from the supply means and forming a stable microjet due to interaction with surrounding air flow focusing the microjet to flow out of an exit of the pressure chamber.

Formation of the microjet and its acceleration and ultimate particle formation are based on the abrupt pressure drop associated with the steep acceleration experienced by the first fluid (e.g., a liquid) on passing through an exit orifice of the pressure chamber which holds the second fluid. On leaving the chamber the flow undergoes a certain pressure  
5 difference between the first fluid (e.g., a liquid) and the second fluid (e.g., a gas), which in turn produces a highly curved zone on the first fluid (e.g., liquid) surface near the exit port of the pressure chamber and in the formation of a cuspidal point from which a steady microjet flows provided the amount of the first fluid (e.g., the liquid) withdrawn through the exit port of the pressure chamber is replenished. Thus, in the same way that a glass lens  
10 or a lens of the eye focuses light to a given point, the flow of the gas surrounds and focuses the liquid into a stable microjet. The focusing effect of the surrounding flow of gas creates a stream of liquid which is substantially smaller in diameter than the diameter of the exit orifice of the pressure chamber. This allows liquid to flow out of the pressure chamber orifice without touching the orifice, providing advantages including (1) clogging of the exit  
15 orifice is virtually eliminated, (2) contamination of flow due to contact with substances (e.g. bacteria) on the orifice opening is virtually eliminated, and (3) the diameter of the stream and the resulting particles are smaller than the diameter of the exit orifice of the chamber. This is particularly desirable because it is difficult to precisely engineer holes which are very small in diameter. Further, in the absence of the focusing effect (and formation a  
20 stable microjet) flow of liquid out of an opening will result in particles which have about twice the diameter of the exit opening. An additional advantage is that the particles are not prone to agglomeration following exit from the chamber owing to the accelerating effect of the surrounding gas stream, which has a velocity larger than the liquid velocity.

Specific embodiments of aerosol creation devices are now described.

25

#### EMBODIMENT OF FIGURE 1

A first embodiment of the invention where the supply means is a cylindrical feeding needle supplying liquid into a pressurized chamber of gas is described below with reference to Figure 1.

30

The components of the embodiment of Figure 1 are as follows:

1. Feeding needle - also referred to generally as a fluid source and a tube.
2. End of the feeding needle used to insert the liquid to be atomized.

3. Pressure chamber.
  4. Orifice used as gas inlet.
  5. End of the feeding needle used to evacuate the liquid to be atomized.
  6. Orifice through which withdrawal takes place.
  7. Atomizate (spray) - also referred to as aerosol.
- $D_f$  = diameter of the feeding needle;  $D_o$  = diameter of the orifice through which the microjet is passed;  $e$  = axial length of the orifice through which withdrawal takes place;  $H$  = distance from the feeding needle to the microjet outlet;  $P_o$  = pressure inside the chamber;  $P_a$  = atmospheric pressure.

An aerosolized drug delivery device of the invention may be any size but is preferably designed to be a hand-held, portable, self-contained device weighing less than 1 kilogram. Although the device can be configured in a variety of designs, the different designs will all include the essential components shown in Figure 1 or components which perform an equivalent function and obtain the desired results. Specifically, a drug delivery device of the invention will be comprised of at least one source of formulation (e.g., a feeding needle with an opening 2) into which a liquid flowable formulation can be fed and an exit opening 5 from which the formulation can be expelled. The feeding needle 1, or at least its exit opening 5, is encompassed by a pressure chamber 3. The chamber 3 has inlet opening 4 which is used to feed gas into the chamber 3 and an exit opening 6 through which gas from the pressure chamber and liquid formulation from the feeding needle 3 are expelled creating an aerosol.

In Figure 1, the feeding needle and pressure chamber are configured to obtain a desired result of producing an aerosol wherein the particles are small and uniform in size. Preferably the particles have a size which is in a range of 0.1 to 10 microns, more preferably 1 to 5 microns. Particles of less than 1 micron in diameter can be produced via the present invention. However, particles below 1 micron may be too small for inhalation as the particles may not settle in the lung during a normal breath hold and as such would be exhaled. The particles of any given aerosol all have about the same diameter with a relative standard deviation of 10% to 30% or more preferably 3% to 20%. Stating that particles of the aerosol have a particle diameter in a range of 1 to 5 microns does not mean that different particles will have different diameters and that some will have a diameter of 1 micron while

others of 5 microns. The particles in a given aerosol will all (preferably about 90% or more) have the same diameter  $\pm 3\%$  to  $\pm 30\%$ . For example, the particles of a given aerosol will have a diameter of 2 microns  $\pm 3\%$  to  $\pm 10\%$ .

Such a monodisperse aerosol is created using the components and configuration as described above. However, other components and configurations will occur to those skilled in the art. The object of each design will be to supply formulation so that it creates a stable capillary microjet which is accelerated and stabilized by tangential viscous stress exerted by the gas on the liquid surface. The stable microjet created by the gas leaves the area of the pressurized gas (e.g., leaves the pressure chamber and exits the pressure chamber orifice) and splits into particles which have the desired size and uniformity.

The aerosol created is a monodisperse aerosol meaning that the size of the particles produced are relatively uniform in size. The relative standard deviation in particle size is in the range of from about 10% to about 30%, preferably 3% to 10% and most preferably 3% or less. The size of aerosolized particles useful for inhalation is a diameter in the range of from about 0.1 micron to about 10 microns, more preferably about 1 micron to about 3 microns.

For purposes of simplicity the remainder of the detailed description of the operation of the device of Figure 1 will refer to the first fluid as liquid and the second fluid as gas. The parameter window used (*i.e.* the set of special values for the liquid properties, flow-rate used, feeding needle diameter, orifice diameter, pressure ratio, *etc.*) should be large enough to be compatible with virtually any liquid (dynamic viscosities in the range from  $10^{-4}$  to  $1 \text{ kg m}^{-1}\text{s}^{-1}$ ); in this way, the capillary microjet that emerges from the end of the feeding needle is absolutely stable and perturbations produced by breakage of the jet cannot travel upstream. Downstream, the microjet splits into evenly shaped drops simply by effect of capillary instability (see, for example, Rayleigh, "On the instability of jets", Proc. London Math. Soc., 4-13, 1878), similar in a manner to a laminar capillary jet falling from a half-open tap.

When the stationary, steady interface is created, the capillary jet that emerges from the end of the drop at the outlet of the feeding point is concentrically withdrawn into the nozzle. After the jet emerges from the drop, the liquid is accelerated by tangential sweeping forces exerted by the gas stream flowing on its surface, which gradually decreases the jet cross-section. Stated differently the gas flow acts as a lens and focuses and stabilizes the microjet as it moves toward and into the exit orifice of the pressure chamber.

The forces exerted by the second fluid (e.g., a gas) flow on the first fluid (e.g., a liquid) surface should be steady enough to prevent irregular surface oscillations. Therefore, any turbulence in the gas motion should be avoided; even if the gas velocity is high, the characteristic size of the orifice should ensure that the gas motion is laminar (similar to the boundary layers formed on the jet and on the inner surface of the nozzle or hole).

### STABLE CAPILLARY MICROJET

Figure 4 illustrates the interaction of a liquid and a gas to form atomizate using the method of the invention. The feeding needle 60 has a circular exit opening 61 with an internal radius  $R_1$  which feeds a liquid 62 out of the end, forming a drop with a radius in the range of  $R_1$  to  $R_1$  plus the thickness of the wall of the needle. Thereafter, the drop narrows in circumference to a much smaller circumference as is shown in the expanded view of the tube (i.e. feeding needle) 5 as shown in Figures 1 and 4. The exiting liquid flow comprises an infinite amount of liquid streamlines 63 that after interaction of the liquid with the surrounding gas to form a stable cusp at the interface 64 of the two fluids. The surrounding gas also forms an infinite number of gas streamlines 65, which interact with the solid surfaces and the exiting liquid to create the effect of a virtual focusing funnel 66. The exiting liquid is focused by the focusing funnel 66 resulting in a stable capillary microjet 67, which remains stable until it exits the opening 68 of the pressure chamber 69. After exiting the pressure chamber, the microjet begins to break-up, forming monodispersed particles 70.

The gas flow, which affects the liquid withdrawal and its subsequent acceleration after the jet is formed, should be very rapid but also uniform in order to avoid perturbing the fragile capillary interface (the surface of the drop that emerges from the jet).

As illustrated in Figure 4, the exit opening 61 of the capillary tube 60 is positioned close to an exit opening 68 in a planar surface of a pressure chamber 69. The exit opening 68 has a minimum diameter  $D_0$  and is in a planar member with a thickness  $e$ . The diameter  $D_0$  is referred to as a minimum diameter because the opening may have a conical configuration with the narrower end of the cone positioned closer to the source of liquid flow. Thus, the exit opening may be a funnel-shaped nozzle although other opening configurations are also possible, e.g. an hour glass configuration. Gas in the pressure chamber continuously flows out of the exit opening. The flow of the gas causes the liquid drop expelled from the tube to



decrease in circumference as the liquid moves away from the end of the tube in a direction toward the exit opening of the pressure chamber.

In actual use, it can be understood that the opening shape which provokes maximum gas acceleration (and consequently the most stable cusp and microjet with a given set of parameters) is a conically shaped opening in the pressure chamber. The conical opening is positioned with its narrower end toward the source of liquid flow.

The distance between the end 61 of the tube 60 and the beginning of the exit opening 68 is H. At this point it is noted that  $R_1$ ,  $D_0$ , H and e are all preferably on the order of hundreds of microns. For example,  $R_1 = 400\mu\text{m}$ ,  $D_0 = 150\mu\text{m}$ ,  $H = 1\text{mm}$ ,  $e = 300\mu\text{m}$ .

However, each could be 1/100 to 10x these sizes.

The end of the liquid stream develops a cusp-like shape at a critical distance from the exit opening 68 in the pressure chamber 69 when the applied pressure drop  $\Delta P_g$  through the exit opening 68 overcomes the liquid-gas surface tension stresses  $\gamma/R^*$  appearing at the point of maximum curvature — e.g.  $1/R^*$  from the exit opening.

A steady state is then established if the liquid flow rate Q ejected from the drop cusp is steadily supplied from the capillary tube. This is the stable capillary cusp which is an essential characteristic of the invention needed to form the stable microjet. More particularly, a steady, thin liquid jet with a typical diameter  $d_j$  is smoothly emitted from the stable cusp-like drop shape and this thin liquid jet extends over a distance in the range of microns to millimeters. The length of the stable microjet will vary from very short (e.g. 1 micron) to very long (e.g. 50 mm) with the length depending on the (1) flow-rate of the liquid and (2) the Reynolds number of the gas stream flowing out of the exit opening of the pressure chamber. The liquid jet is the stable capillary microjet obtained when supercritical flow is reached. This jet demonstrates a robust behavior provided that the pressure drop  $\Delta P_g$  applied to the gas is sufficiently large compared to the maximum surface tension stress (on the order of  $\gamma/d_j$ ) that act at the liquid-gas interface. The jet has a slightly parabolic axial velocity profile which is, in large part, responsible for the stability of the microjet. The stable microjet is formed without the need for other forces, i.e. without adding force such as electrical forces on a charged fluid. However, for some applications it is preferable to add charge to particles, e.g. to cause the particles to adhere to a given surface. The shaping of liquid exiting the capillary tube by the gas flow forming a focusing funnel creates a cusp-like meniscus resulting in the stable microjet. This is a fundamental characteristic of the invention.

The stable capillary microjet is maintained stably for a significant distance in the direction of flow away from the exit from the tube. The liquid is, at this point, undergoing "supercritical flow." The microjet eventually destabilizes due to the effect of surface tension forces. Destabilization results from small natural perturbations moving downstream, with the fastest growing perturbations being those which govern the break up of the microjet, eventually creating a uniform sized monodisperse aerosol 70 as shown in Figure 4.

The microjet, even as it initially destabilizes, passes out of the exit orifice of the pressure chamber without touching the peripheral surface of the exit opening. This provides an important advantage of the invention which is that the exit opening 68 (which could be referred to as a nozzle) will not clog from residue and/or deposits of the liquid. Clogging is a major problem with very small nozzles and is generally dealt with by cleaning or replacing the nozzle. When fluid contacts the surfaces of a nozzle opening some fluid will remain in contact with the nozzle when the flow of fluid is shut off. The liquid remaining on the nozzle surface evaporates leaving a residue. After many uses over time the residue builds up and clogging takes place. The present invention substantially reduces or eliminates this clogging problem.

### MATHEMATICS OF A STABLE MICROJET

Cylindrical coordinates (r,z) are chosen for analyzing the shape of a stable microjet, i.e. a liquid jet undergoing "supercritical flow." The cusp-like meniscus formed by the liquid coming out of the tube is pulled toward the exit of the pressure chamber by a pressure gradient created by the flow of gas.

The cusp-like meniscus formed at the tube's mouth is pulled towards the hole by the pressure gradient created by the gas stream. From the cusp of this meniscus, a steady liquid thread with the shape of radius  $r = \xi$  is withdrawn through the hole by the action of both the suction effect due to  $\Delta P_g$  and the tangential viscous stresses  $\tau_s$  exerted by the gas on the jet's surface in the axial direction. The averaged momentum equation for this configuration may be written:

$$\frac{d}{dz} \left[ P_1 + \frac{\rho_1 Q^2}{2\pi^2 \xi^4} \right] = \frac{2\tau_s}{\xi}, \quad (1)$$

where  $Q$  is the liquid flow rate upon exiting the feeding tube,  $P_1$  is the liquid pressure, and  $\rho_1$  is the liquid density, assuming that the viscous extensional term is negligible compared to the kinetic energy term, as will be subsequently justified. In addition, liquid evaporation effects are neglected. The liquid pressure  $P_1$  is given by the capillary equation.

$$P_1 = P_g + \gamma/\xi. \quad (2)$$

- 5 where  $\gamma$  is the liquid-gas surface tension. As shown in the Examples, the pressure drop  $\Delta P_g$  is sufficiently large as compared to the surface tension stress  $\gamma/\xi$  to justify neglecting the latter in the analysis. This scenario holds for the whole range of flow rates in which the microjet is absolutely stable. In fact, it will be shown that, for a given pressure drop  $\Delta P_g$ , the minimum liquid flow rate that can be sprayed in steady jet conditions is achieved when the surface
- 10 stress  $\gamma/\xi$  is of the order of the kinetic energy of the liquid  $\rho_1 Q^2/(2\pi^2 \xi^4)$ , since the surface tension acts like a "resistance" to the motion (it appears as a *negative* term in the right-hand side term of Eq. (1)). Thus,

$$Q_{min} \sim \left( \frac{\gamma d_j^3}{\rho_1} \right)^{1/2} \quad (3)$$

For sufficiently large flow rates  $Q$  compared to  $Q_{min}$ , the simplified averaged momentum equation in the axial direction can be expressed as

15

$$\frac{d}{dz} \left( \frac{\rho_1 Q^2}{2\pi^2 \xi^4} \right) = \frac{dP_g}{dz} + \frac{2\tau_s}{\xi}, \quad (4)$$

- where one can identify the two driving forces for the liquid flow on the right-hand side. This equation can be integrated provided the following simplification is made: if one uses a thin plate with thickness  $L$  of the order or smaller than the hole's diameter  $D$  (which minimizes downstream perturbations in the gas flow), the pressure gradient up to the hole exit is on the
- 20 average much larger than the viscous shear term  $2\tau_s/\xi$  owing to the surface stress. On the other hand, the axial viscous term is of the order  $O[\mu^2 Q/D^2 d_j^2]$ , since the hole diameter  $D$  is

actually the characteristic distance associated with the gas flow at the hole's entrance in both the radial and axial directions. This term is very small compared to the pressure gradient in real situations, provided that  $\Delta P_g \gg \mu^2/D^2\rho_1$  (which holds, e.g., for liquids with viscosities as large as 100 cpoises, using hole diameters and pressure drops as small as  $D \sim 10 \mu\text{m}$  and  $\Delta P_g \geq 100$  mbar). The neglect of all viscous terms in Eq. (4) is then justified. Notice that in this limit on the liquid flow is *quasi-isentropic* in the average (the liquid almost follows Bernoulli equation) as opposed to most micrometric extensional flows. Thus, integrating (4) from the stagnation regions of both fluids up to the exit, one obtains a *simple* and *universal* expression for the jet diameter at the hole exit:

$$d_j \approx \left( \frac{8\rho_1}{\Pi^2 \Delta P_g} \right)^{1/4} Q^{1/2}, \quad (5)$$

which for a given pressure drop  $\Delta P_g$  is *independent* of geometrical parameters (hole and tube diameters, tube-hole distance, etc.), liquid and gas viscosities, and liquid-gas surface tension. This diameter remains almost constant up to the breakup point since the gas pressure after the exit remains constant.

## 15 MONODISPERSE PARTICLES

Above the stable microjet undergoing "supercritical flow" is described and it can be seen how this aspect of the invention can be made use of in a variety of industrial applications -- particularly where the flow of liquid through small holes creates a clogging problem. An equally important aspect of the invention is obtained after the microjet leaves the pressure chamber.

When the microjet exits the pressure chamber the liquid pressure  $P_1$  becomes (like the gas pressure  $P_g$ ) almost constant in the axial direction, and the jet diameter remains almost constant up to the point where it breaks up by capillary instability. Defining a Weber number  $We = (\rho_g v_g^2 d_j)/\gamma \approx 2 \Delta P_g d_j/\gamma$  (where  $v_g$  is the gas velocity measured at the orifice), below a certain experimental value  $We_c \sim 40$  the breakup mode is axisymmetric and the resulting droplet stream is characterized by its *monodispersity* provided that the fluctuations of the gas flow do not contribute to droplet coalescence (these fluctuations occur when the gas stream reaches a fully developed turbulent profile around the liquid jet breakup region). Above this

We<sub>c</sub> value, sinuous nonaxisymmetric disturbances, coupled to the axisymmetric ones, become apparent. For larger We numbers, the nonlinear growth rate of the sinuous disturbances seems to overcome that of the axisymmetric disturbances. The resulting spray shows significant polydispersity in this case. Thus, it can be seen that by controlling parameters to keep the  
5 resulting Weber number to 40 or less, allows the particles formed to be all substantially the same size. The size variation is about  $\pm 3\%$  to  $\pm 30\%$  and move preferably  $\pm 3\%$  to  $\pm 10\%$ . These particles can have a desired size e.g. 0.1 microns to 50 microns.

The shed vorticity influences the breakup of the jet and thus the formation of the particles. Upstream from the hole exit, in the accelerating region, the gas stream is laminar.  
10 Typical values of the Reynolds number range from 500 to 6000 if a velocity of the order of the speed of sound is taken as characteristic of the velocity of the gas. Downstream from the hole exit, the cylindrical mixing layer between the gas stream and the stagnant gas becomes unstable by the classical Kelvin-Helmholtz instability. The growth rate of the thickness of this layer depends on the Reynolds number of the flow and ring vortices are formed at a frequency  
15 of the order of  $v_g/D$ , where  $D$  is the hole diameter. Typical values of  $v_g$  and  $D$  as those found in our experimental technique lead to frequencies of the order of MHz which are comparable to the frequency of drop production (of order of  $t_b^{-1}$ ).

Given the liquid flow rate and the hole diameter, a resonance frequency which depends on the gas velocity (or pressure difference driving the gas stream) can be adjusted  
20 (*tuned*) in such a way that vortices act as a forcing system to excite perturbations of a determined wavelength on the jet surface. Experimental results obtained clearly illustrates the different degree of coupling between the two gas-liquid coaxial jets. In one set of experimental results the particle sizes are shown to have a particle size of about 5.7 microns with a standard deviation of 12%. This results when the velocity of the gas has been properly  
25 tuned to minimize the dispersion in the size of droplets resulting from the jet breakup. In this case, the flow rate of the liquid jet and its diameter are  $0.08 \mu\text{l s}^{-1}$  and  $3 \mu\text{m}$ , respectively. Data have been collected using a MASTERSIZER from MALVERN Instruments. As the degree of coupling decreases, perturbations at the jet surface of different wavelengths become excited and, as it can be observed from the size distributions, the dispersion of the spray increases.

30 It is highly desirable in a number of different industrial applications to have particles which are uniform in size or to create aerosols of liquid particles which are uniform in size. For example, particles of a liquid formation containing a pharmaceutically active drug

could be created and designed to have a diameter of about 2 microns  $\pm 3\%$ . These particles could be inhaled into the lungs of a patient for intrapulmonary drug delivery. Moreover, particle size can be adjusted to target a particular area of the respiratory tract.

Upstream of the orifice exit the gas flow should be laminar in order to avoid a  
 5 turbulent regime - turbulent fluctuations in the gas flow which have a high frequency and would perturb the liquid-gas interface. The Reynolds numbers reached at the orifice are

$$Re = \frac{v_g d_0}{\nu_g} \sim 4000$$

where  $\nu_g$  is the kinematic viscosity of the gas. Even though this number is quite high, there are large pressure gradients downstream (a highly convergent geometry), so that a turbulent regime is very unlikely to develop.

10 The essential difference from existing pneumatic atomizers (which possess large Weber numbers) and the present invention is that the aim of the present invention is not to rupture the liquid-gas interface but the opposite, i.e. to increase the stability of the interface until a capillary jet is obtained. The jet, which will be very thin provided the pressure drop resulting from withdrawal is high enough, splits into drops the sizes of which are much more  
 15 uniform than those resulting from disorderly breakage of the liquid-gas interface in existing pneumatic atomizers.

The proposed atomization system obviously requires delivery of the liquid to be atomized and the gas to be used in the resulting spray. Both should be fed at a rate ensuring that the system lies within the stable parameter window. Multiplexing is effective when the  
 20 flow-rates needed exceed those on an individual cell. More specifically, a plurality of feeding sources or feeding needles may be used to increase the rate at which aerosols are created. The flow-rates used should also ensure the mass ratio between the flows is compatible with the specifications of each application.

The gas and liquid can be dispensed by any type of continuous delivery system (*e.g.*  
 25 a compressor or a pressurized tank the former and a volumetric pump or a pressurized bottle the latter). If multiplexing is needed, the liquid flow-rate should be as uniform as possible among cells; this may entail propulsion through several capillary needles, porous media or any other medium capable of distributing a uniform flow among different feeding points.

Each individual atomization device should consist of a feeding point (a capillary needle, a point with an open microchannel, a microprotuberance on a continuous edge, *etc.*) 0.002-2 mm (but, preferentially 0.01-0.4 mm) in diameter, where the drop emerging from the microjet can be anchored, and a small orifice 0.002-2 mm (preferentially 0.01-0.25 mm) in diameter facing the drop and separated 0.01-2 mm (preferentially 0.2-0.5 mm) from the feeding point. The orifice communicates the withdrawal gas around the drop, at an increased pressure, with the zone where the atomize is produced, at a decreased pressure. The atomizer can be made from a variety of materials (metal, polymers, ceramics, glass).

Figure 1 depicts a tested prototype where the liquid to be atomized is inserted through one end of the system 2 and the propelling gas is introduced via the special inlet 4 in the pressure chamber 3. The prototype was tested at gas feeding rates from 100 to 2000 mBar above the atmospheric pressure  $P_a$  at which the atomized liquid was discharged. The whole enclosure around the feeding needle 1 was at a pressure  $P_o > P_a$ . The liquid feeding pressure,  $P_l$ , should always be slightly higher than the gas propelling pressure,  $P_o$ . Depending on the pressure drop in the needle and the liquid feeding system, the pressure difference ( $P_l - P_o > 0$ ) and the flow-rate of the liquid to be atomized,  $Q$ , are linearly related provided the flow is laminar - which is indeed the case with this prototype. The critical dimensions are the distance from the needle to the plate ( $H$ ), the needle diameter ( $D_o$ ), the diameter of the orifice through which the microjet 6 is discharged ( $d_o$ ) and the axial length,  $e$ , of the orifice (*i.e.* the thickness of the plate where the orifice is made). In this prototype,  $H$  was varied from 0.3 to 0.7 mm on constancy of the distances ( $D_o = 0.45$  mm,  $d_o = 0.2$  mm) and  $e = 0.5$  mm. The quality of the resulting spray 7 did not vary appreciably with changes in  $H$  provided the operating regime (*i.e.* stationary drop and microjet) was maintained. However, the system stability suffered at the longer  $H$  distances (about 0.7 mm). The other atomizer dimensions had no effect on the spray or the prototype functioning provided the zone around the needle (its diameter) was large enough relative to the feeding needle.

### WEBER NUMBER

Adjusting parameters to obtain a stable capillary microjet and control its breakup into monodisperse particle is governed by the Weber number and the liquid-to-gas velocity ratio or  $\alpha$  which equal  $V_l/V_g$ . The Weber number or "We" is defined by the following equation:

$$We = \frac{\rho_g V_g^2 d}{\gamma}$$

wherein  $\rho_g$  is the density of the gas,  $d$  is the diameter of the stable microjet,  $\gamma$  is the liquid-gas surface tension, and  $V_g^2$  is the velocity of the gas squared.

When carrying out the invention the parameters should be adjusted so that the Weber number is greater than 1 in order to produce a stable capillary microjet. However, to obtain a particle dispersion which is monodisperse (i.e. each particle has the same size  $\pm 3$  to  $\pm 30\%$ ) the parameters should be adjusted so that the Weber number is less than about 40. The monodisperse aerosol is obtained with a Weber number in a range of about 1 to about 40 ( $1 \leq We \leq 40$ ).

10

#### OHNESORGE NUMBER

A measure of the relative importance of viscosity on the jet breakup can be estimated from the Ohnesorge number defined as the ratio between two characteristic times: the viscous time  $t_v$  and the breaking time  $t_b$ . The breaking time  $t_b$  is given by [see Rayleigh (1878)]

$$t_b \sim \left( \frac{\rho d^2}{\gamma} \right)^{1/2}. \quad (2)$$

15 Perturbations on the jet surface are propagated inside by viscous diffusion in times  $t_v$  of the order of

$$t_v \sim \rho d^2 / \mu_1, \quad (3)$$

where  $\mu_1$  is the viscosity of the liquid. Then, the Ohnesorge number,  $Oh$ , results

$$Oh = \frac{\mu_1}{(\rho \gamma d)^{1/2}}. \quad (4)$$



If this ratio is much smaller than unity viscosity plays no essential role in the phenomenon under consideration. Since the maximum value of the Ohnesorge number in actual experiments conducted is as low as  $3.7 \times 10^{-2}$ , viscosity plays no essential role during the process of jet breakup.

5

## EMBODIMENT OF FIGURE 2

A variety of configurations of components and types of fluids will become apparent to those skilled in the art upon reading this disclosure. These configurations and fluids are encompassed by the present invention provided they can produce a stable capillary microjet of  
10 a first fluid from a source to an exit port of a pressure chamber containing a second fluid. The stable microjet is formed by the first fluid flowing from the feeding source to the exit port of the pressure chamber being accelerated and stabilized by tangential viscous stress exerted by the second fluid in the pressure chamber on the surface of the first fluid forming the microjet. The second fluid forms a focusing funnel when a variety of parameters are correctly tuned or  
15 adjusted. For example, the speed, pressure, viscosity and miscibility of the first and second fluids are chosen to obtain the desired results of a stable microjet of the first fluid focused into the center of a funnel formed with the second fluid. These results are also obtained by adjusting or tuning physical parameters of the device, including the size of the opening from which the first fluid flows, the size of the opening from which both fluids exit, and the  
20 distance between these two openings.

The embodiment of Figure 1 can, itself, be arranged in a variety of configurations. Further, as indicated above, the embodiment may include a plurality of feeding needles. A plurality of feeding needles may be configured concentrically in a single construct, as shown in Figure 2.

25 The components of the embodiment of Figure 2 are as follows:

21. Feeding needle - tube or source of fluid.
22. End of the feeding needle used to insert the liquids to be atomized.
23. Pressure chamber.
24. Orifice used as gas inlet.
- 30 25. End of the feeding needle used to evacuate the liquid to be atomized.
26. Orifice through which withdrawal takes place.
27. Atomizate (spray) or aerosol.

- 28. First liquid to be atomized (inner core of particle).
  - 29. Second liquid to be atomized (outer coating of particle).
  - 30. Gas for creation of microjet.
  - 31. Internal tube of feeding needle.
  - 5 32. External tube of feeding needle.
- $D$  = diameter of the feeding needle;  $d$  = diameter of the orifice through which the microjet is passed;  $e$  = axial length of the orifice through which withdrawal takes place;  $H$  = distance from the feeding needle to the microjet outlet;  $\gamma$  = surface tension;  $P_o$  = pressure inside the chamber;  $P_a$  = atmospheric pressure.

The embodiment of Figure 2 is preferably used when attempting to form a spherical particle of one substance coated by another substance. The device of Figure 2 is comprised of the same basic component as per the device of Figure 1 and further includes a second feeding source 32 which is positioned concentrically around the first cylindrical feeding source 31. The second feeding source may be surrounded by one or more additional feeding sources with each concentrically positioned around the preceding source. The outer coating may be used for a variety of purposes, including: coating particles to prevent small particles from sticking together; to obtain a sustained release effect of the active compound (e.g. a pharmaceutically active drug) inside, and/or to mask flavors; and to protect the stability of another compound (e.g. a pharmaceutically active drug) contained therein.

The process is based on the microsuction which the liquid-gas or liquid-liquid interphase undergoes (if both are immiscible), when said interphase approaches a point beginning from which one of the fluids is suctioned off while the combined suction of the two fluids is produced. The interaction causes the fluid physically surrounded by the other to form a capillary microjet which finally breaks into spherical drops. If instead of two fluids (gas-liquid), three or more are used that flow in a concentric manner by injection using concentric tubes, a capillary jet composed of two or more layers of different fluids is formed which, when it breaks, gives rise to the formation of spheres composed of several approximately concentric spherical layers of different fluids. The size of the outer sphere (its thickness) and the size of the inner sphere (its volume) can be precisely adjusted. This can allow the manufacture of coated particles for a variety of end uses. For example the thickness

of the coating can be varied in different manufacturing events to obtain coated particles which have gradually decreasing thicknesses to obtain a controlled release effect of the contents, e.g. a pharmaceutically active drug. The coating could merely prevent the particles from degrading, reacting, or sticking together.

5           The method is based on the breaking of a capillary microjet composed of a nucleus of one liquid or gas and surrounded by another or other liquids and gases which are in a concentric manner injected by a special injection head, in such a way that they form a stable capillary microjet and that they do not mix by diffusion during the time between when the microjet is formed and when it is broken. When the capillary microjet is broken into spherical  
10 drops under the proper operating conditions, which will be described in detail below, these drops exhibit a spherical nucleus, the size and eccentricity of which can be controlled.

          In the case of spheres containing two materials, the injection head 25 consists of two concentric tubes with an external diameter on the order of one millimeter. Through the internal tube 31 is injected the material that will constitute the nucleus of the microsphere,  
15 while between the internal tube 31 and the external tube 32 the coating is injected. The fluid of the external tube 32 joins with the fluid of tube 31 as the fluids exit the feeding needle, and the fluids (normally liquids) thus injected are accelerated by a stream of gas that passes through a small orifice 24 facing the end of the injection tubes. When the drop in pressure across the orifice 24 is sufficient, the liquids form a completely stationary capillary microjet,  
20 if the quantities of liquids that are injected are stationary. This microjet does not touch the walls of the orifice, but passes through it wrapped in the stream of gas or funnel formed by gas from the tube 32. Because the funnel of gas focuses the liquid, the size of the exit orifice 26 does not dictate the size of the particles formed.

          When the parameters are correctly adjusted, the movement of the liquid is uniform  
25 at the exit of the orifice 26 and the viscosity forces are sufficiently small so as not to alter either the flow or the properties of the liquids; for example, if there are biochemical molecular specimens having a certain complexity and fragility, the viscous forces that would appear in association with the flow through a micro-orifice might degrade these substances.

          Figure 2 shows a simplified diagram of the feeding needle 21, which is comprised  
30 of the concentric tubes 30, 31 through the internal and external flows of the fluids 28, 29 that are going to compose the microspheres comprised of two immiscible fluids. The difference in pressures  $P_0 - P_a$  ( $P_0 > P_a$ ) through the orifice 26 establishes a flow of gas present in the

chamber 23 and which is going to surround the microjet at its exit. The same pressure gradient that moves the gas is the one that moves the microjet in an axial direction through the hole 26, provided that the difference in pressures  $P_0 - P_\alpha$  is sufficiently great in comparison with the forces of surface tension, which create an adverse gradient in the direction of the movement.

There are two limitations for the minimum sizes of the inside and outside jets that are dependent (a) on the surface tensions  $\gamma_1$  of the outside liquid 29 with the gas 30 and  $\gamma_2$  of the outside liquid 29 with the inside liquid 28, and (b) on the difference in pressures  $\Delta P = P_0 - P_\alpha$  through the orifice 26. In the first place, the jump in pressures  $\Delta P$  must be sufficiently great so that the adverse effects of the surface tension are minimized. This, however, is attained for very modest pressure increases: for example, for a 10 micron jet of a liquid having a surface tension of 0.05 N/m (tap water), the necessary minimum jump in pressure is in the order of  $0.05 \text{ (N/m)} / 0.00001 \text{ m} = \Delta P = 50 \text{ mBar}$ . But, in addition, the breakage of the microjet must be regular and axilsymmetric, so that the drops will have a uniform size, while the extra pressure  $\Delta P$  cannot be greater than a certain value that is dependent on the surface tension of the outside liquid with the gas  $\gamma_1$  and on the outside diameter of the microjet. It has been experimentally shown that this difference in pressures cannot be greater than 20 times the surface tension  $\gamma_1$  divided by the outside radius of the microjet.

Therefore, given some inside and outside diameters of the microjet, there is a range of operating pressures between a minimum and a maximum; nonetheless, experimentally the best results are obtained for pressures in the order of two to three times the minimum.

The viscosity values of the liquids must be such that the liquid with the greater viscosity  $\mu_{\max}$  verifies, for a diameter  $d$  of the jet predicted for this liquid and a difference through the orifice  $\Delta P$ , the inequality:

25

$$\mu_{\max} \leq \frac{\Delta P d^2 D}{Q}$$

With this, the pressure gradients can overcome the extensional forces of viscous resistance exerted by the liquid when it is suctioned toward the orifice.

Moreover, the liquids must have very similar densities in order to achieve the concentricity of the nucleus of the microsphere, since the relation of velocities between the liquids moves according to the square root of the densities  $v_1/v_2 = (\rho_2/\rho_1)^{1/2}$  and both jets, the

inside jet and the outside jet, must assume the most symmetrical configuration possible, which does not occur if the liquids have different velocities (Figure 2). Nonetheless, it has been experimentally demonstrated that, on account of the surface tension  $\gamma_2$  between the two liquids, the nucleus tends to migrate toward the center of the microsphere, within prescribed  
5 parameters.

When two liquids and gas are used on the outside, the distance between the planes of the mouths of the concentric tubes can vary, without the characteristics of the jet being substantially altered, provided that the internal tube 31 is not introduced into the external one 32 more than one diameter of the external tube 32 and provided that the internal tube 31 does  
10 not project more than two diameters from the external tube 32. The best results are obtained when the internal tube 31 projects from the external one 32 a distance substantially the same as the diameter of the internal tube 31. This same criterion is valid if more than two tubes are used, with the tube that is surrounded (inner tube) projecting beyond the tube that surrounds (outer tube) by a distance substantially the same as the diameter of the first tube.

15 The distance between the plane of the internal tube 31 (the one that will normally project more) and the plane of the orifice may vary between zero and three outside diameters of the external tube 32, depending on the surface tensions between the liquids and with the gas, and on their viscosity values. Typically, the optimal distance is found experimentally for each particular configuration and each set of liquids used.

20 The proposed atomizing system obviously requires fluids that are going to be used in the resulting spray to have certain flow parameters. Accordingly, flows for this use must be:

- Flows that are suitable so that the system falls within the parametric window of stability. Multiplexing (i.e. several sets of concentric tubes) may be used, if the flows  
25 required are greater than those of an individual cell.

- Flows that are suitable so that the mass relation of the fluids falls within the specifications of each application. Of course, a greater flow of gas may be supplied externally by any means in specific applications, since this does not interfere with the functioning of the atomizer.

30 Therefore, any means for continuous supply of gas (compressors, pressure deposits, etc.) and of liquid (volumetric pumps, pressure bottles) may be used. If multiplexing is desired, the flow of liquid must be as homogeneous as possible between the

various cells, which may require impulse through multiple capillary needles, porous media, or any other medium capable of distributing a homogeneous flow among different feeding points.

Each atomizing device will consist of concentric tubes 31, 32 with a diameter  
5 ranging between 0.05 and 2 mm, preferably between 0.1 and 0.4 mm, on which the drop  
from which the microjet emanates can be anchored, and a small orifice (between 0.001 and  
2 mm in diameter, preferably between 0.1 and 0.25 mm), facing the drop and separated from  
the point of feeding by a distance between 0.001 and 2 mm, preferably between 0.2 and 0.5  
mm. The orifice puts the suction gas that surrounds the drop, at higher pressure, in touch  
10 with the area in which the atomizing is to be attained, at lower pressure.

### EMBODIMENT OF FIGURE 3

The embodiments of Figures 1 and 2 are similar in a number of ways. Both have  
a feeding piece which is preferably in the form of a feeding needle with a circular exit  
15 opening. Further, both have an exit port in the pressure chamber which is positioned  
directly in front of the flow path of fluid out of the feeding source. Precisely maintaining  
the alignment of the flow path of the feeding source with the exit port of the pressure  
chamber can present an engineering challenge particularly when the device includes a  
number of feeding needles. The embodiment of Figure 3 is designed to simplify the manner  
20 in which components are aligned. The embodiment of Figure 3 uses a planar feeding piece,  
which by virtue of the withdrawal effect produced by the pressure difference across a small  
opening through which fluid is passed permits multiple microjets to be expelled through  
multiple exit ports of a pressure chamber thereby obtaining multiple aerosol streams.  
Although a single planar feeding member is shown in Figure 3 it, of course, is possible to  
25 produce a device with a plurality of planar feeding members where each planar feeding  
member feeds fluid to a linear array of outlet orifices in the surrounding pressure chamber.  
In addition, the feeding member need not be strictly planar, and may be a curved feeding  
device comprised of two surfaces that maintain approximately the same spatial distance  
between the two pieces of the feeding source. Such curved devices may have any level of  
30 curvature, e.g. circular, semicircular, elliptical, hemi-elliptical etc.

The components of the embodiment of Figure 3 are as follows:

41. Feeding piece.

42. End of the feeding piece used to insert the fluid to be atomized.
43. Pressure chamber.
44. Orifice used as gas inlet.
45. End of the feeding needle used to evacuate the liquid to be atomized.
- 5 46. Orifices through which withdrawal takes place.
47. Atomizate (spray) or aerosol.
48. first fluid containing material to be atomized.
49. second fluid for creation of microjet.
50. wall of the propulsion chamber facing the edge of the feeding piece.
- 10 51. channels for guidance of fluid through feeding piece.
- $d_j$  = diameter of the microjet formed;  $\rho_A$  = liquid density of first fluid (48);  $\rho_B$  = liquid density of second fluid (49);  $v_A$  = velocity of the first liquid (48);  $v_B$  = velocity of the second liquid (49);  $e$  = axial length of the orifice through which withdrawal takes place;  $H$  = distance from the feeding needle to the microjet outlet;  $P_o$  = pressure inside the
- 15 chamber;
- $\Delta p_g$  = change in pressure of the gas;  $P_a$  = atmospheric pressure;  $Q$  = volumetric flow rate

The proposed dispersing device consists of a feeding piece 41 which creates a planar feeding channel through which a where a first fluid 48 flows. The flow is

20 preferably directed through one or more channels of uniform bores that are constructed on the planar surface of the feeding piece 41. A pressure chamber 43 that holds the propelling flow of a second liquid 49, houses the feeding piece 41 and is under a pressure above maintained outside the chamber wall 50. One or more orifices, openings or slots (outlets) 46 made in the wall 52 of the propulsion chamber face the edge of the feeding

25 piece. Preferably, each bore or channel of the feeding piece 41 has its flow path substantially aligned with an outlet 46.

Formation of the microjet and its acceleration are based on the abrupt pressure drop resulting from the steep acceleration undergone by the second fluid 49 on passing through the orifice 46, similarly to the procedure described above for embodiments of

30 Figures 1 and 2 when the second fluid 49 is a gas.

When the second fluid 49 is a gas and the first fluid 48 is a liquid, the microthread formed is quite long and the liquid velocity is much smaller than the gas

velocity. In fact, the low viscosity of the gas allows the liquid to flow at a much lower velocity; as a result, the microjet is actually produced and accelerated by stress forces normal to the liquid surface, i.e. pressure forces. Hence, one effective approximation to the phenomenon is to assume that the pressure difference established will result in the same kinetic energy per unit volume for both fluids (liquid and gas), provided gas compressibility effects are neglected. The diameter  $d_j$  of the microjet formed from a liquid density  $\rho_l$  that passes at a volumetric flow-rate  $Q$  through an orifice across which a pressure difference  $\Delta P_g$  exists will be given by

$$d_j \cong \left( \frac{8\rho_l}{\pi^2 \Delta P_g} \right)^{1/4} Q^{1/2}$$

See Gañán-Calvo, *Physical Review Letters*, 80:285-288 (1998).

The relation between the diameter of the microjet,  $d_j$ , and that of the resulting drops,  $\bar{d}$ , depends on the ratio between viscous forces and surface tension forces on the liquid on the one hand, and between dynamic forces and surface tension forces on the gas on the other (i.e. on the Ohnesorge and Weber numbers, respectively) (Hinds (*Aerosol Technology*, John & Sons, 1982), Lefevre (*Atomization and Sprays*, Hemisphere Pub. Corp., 1989) and Bayvel & Orzechowski (*Liquid Atomization*, Taylor & Francis, 1993)). At moderate to low gas velocities and low viscosities the relation is roughly identical with that for capillarity instability developed by Rayleigh:

$$\bar{d} = 1.89d_j$$

Because the liquid microjet is very long, at high liquid flow-rates the theoretical rupture point lies in the turbulent zone created by the gas jet, so turbulent fluctuations in the gas destabilize or rupture the liquid microjet in a more or less uneven manner. As a result, the benefits of drop size uniformity are lost.

On the other hand, when the second fluid 49 is a liquid and the first fluid 48 is a gas, the facts that the liquid is much more viscous and that the gas is much less dense provide that the gas microthread formed is much shorter; however, because its rupture zone is almost invariably located in a laminar flowing stream, dispersion in the size of the



microbubbles formed is almost always small. At a volumetric gas flow-rate  $Q_g$  and a liquid overpressure  $\Delta P_l$ , the diameter of the gas microjet is given by:

$$d_j \equiv \left( \frac{8\rho_g}{\pi^2 \Delta P_l} \right)^{1/4} Q_g^{1/2}$$

where  $\rho_g$  is the gas density. The low liquid velocity and the absence of relative velocities between the liquid and gas lead to the Rayleigh relation between the diameters of the microthread and those of the bubbles (*i.e.*  $d = 1.89d_j$ ).

If both fluids 48, 49 are liquid and scarcely viscous, then their relative velocities will be given by their densities ratio:

$$\frac{v_A}{v_B} = \left( \frac{\rho_B}{\rho_A} \right)^{1/2}$$

The diameter of a microjet of the first liquid at a volumetric flow-rate of  $Q_A$  and an overpressure of  $\Delta P_B$  will be given by

$$d_j \equiv \left( \frac{8\rho_A}{\pi^2 \Delta P_B} \right)^{1/4} Q_A^{1/2}$$

10 At viscosities such that the velocities of both fluids 48, 49 will rapidly equilibrate in the microjet, the diameter of the microjet of the first liquid will be given by

$$d_j \equiv \left( \frac{8\rho_B}{\pi^2 \Delta P_B} \right)^{1/4} Q_A^{1/2}$$

The proposed atomization system obviously requires delivery of the fluids 48, 49 to be used in the dispersion process at appropriate flow-rates. Thus:

- (1) Both flow-rates should be adjusted for the system so that they lie within the stable parameter window.

- 5 (2) The mass ratio between the flows should be compatible with the specifications of each application. Obviously, the gas flow-rate can be increased by using an external means in special applications (*e.g.* burning, drug inhalation) since this need not interfere with the atomizer operation.
- 10 (3) Therefore, the gas and liquid can be dispensed by any type of continuous delivery system (*e.g.* a compressor or a pressurized tank the former and a volumetric pump or a pressurized bottle the latter).
- (4) The atomizer can be made from a variety of materials (metal, plastic, ceramics, glass).

## 15 BUBBLES INTO LIQUID OR GAS

Figures 6 and 7 are useful in showing how bubbles may be formed in either a liquid (Figure 6) or a gas (Figure 7). In Figure 6 a tubular feeding source 71 is continually supplied with a flow of gas which forms a stable cusp 72 which is surrounded by the flow of liquid 73 in the pressure chamber 74 which is continually supplied with a flow of liquid 73. The liquid 73 flows out of the chamber 74 into a liquid 75 which may be the same as or different from the liquid 73.

The cusp 72 of gas narrows to a capillary supercritical flow 76 and then enter the exit opening 77 of the chamber 74. At a point 78 in the exit opening 77 the supercritical flow 76 begins to destabilize but remains as a critical capillary flow until leaving the exit opening 77. Upon leaving the exit opening 77 the gas stream breaks apart and forms bubbles 79 each of which are substantially identical to the others in shape and size. The uniformity of bubbles is such that one bubble differs from another (in terms of measured physical diameter) in an amount in a range of standard deviation of  $\pm 0.01\%$  to  $\pm 30\%$  with a preferred deviation being less than 1%. Thus, the uniformity in size of the bubbles is greater than the uniformity of the particles formed as described above in connection with Figure 1 when liquid particles are formed.

Gas in the bubbles 79 will diffuse into the liquid 75. Smaller bubbles provide for greater surface area contact with the liquid 75. Smaller bubbles provide for greater surface area contact with the liquid 75 thereby allowing for a faster rate of diffusion than would occur if the same volume of gas were present in a smaller number of bubbles. For example, 5 ten bubbles each containing 1 cubic mm of gas would diffuse gas into the liquid much more rapidly than one bubble containing 10 cubic mm of gas. Further, smaller bubbles rise to the liquid surface more slowly than larger bubbles. A slower rate of ascent in the liquid means that the gas bubbles are in contact with the liquid for a longer period of time thereby increasing the amount of diffusion of gas into the liquid. Thus, smaller bubbles could allow 10 a greater amount of a pharmaceutically active drug to diffuse into a carrier. Because the bubbles are so uniform in size the amount of gas diffusing into the liquid can be uniformly calculated which is important to obtain a uniform concentration of drug in a carrier.

Figure 7 shows the same components as shown in Figure 6 except that the liquid 75 is replaced with a gas 80. When the stream of bubbles 79 disassociate the liquid 73 15 forms an outer spherical cover thereby providing hollow droplets 81 which will float in the gas 80. The hollow droplets 81 have a large physical or actual diameter relative to their aerodynamic diameter. Hollow droplets fall in air at a much slower rate compared to liquid droplets of the same diameter. Because the hollow droplets 81 do not settle or fall quickly in air they can be inhaled into the lungs. Eventually the hollow droplets 81 will burst and 20 form many smaller particles which can be drawn even deeper into the lungs. Thus, it is understood that the aerodynamic diameter of the hollow droplets is very small compared to their actual physical diameter. The creation of hollow droplets 81 which burst and form very small particles is applicable to obtain deeper delivery of drug into the lungs.

## 25 EMULSIONS

Figure 8 is similar to Figures 6 and 7. However, rather than a gas 72 as in Figure 6 the feeding source 71 provides a stream of liquid 82 which may be miscible but is preferably immiscible in the liquid 73. Further the liquid 73 may be the same as or different from the liquid 75 but is preferably immiscible in the liquid 75. The creation of emulsions 30 using such a configuration of liquids has applicability in a variety of fields particularly because the liquid particles formed can have a size in the range of from about 1 to about 200 microns with a standard deviation in size of one particle to another being as little as 0.01%.

The size deviation of one particle to another can vary up to about 30% and is preferably less than  $\pm 5\%$  and more preferably less than  $\pm 1\%$ .

The system operates to expel the liquid 82 out of the exit orifice 77 to form spheres 83 of liquid 82. Each sphere 83 has an actual physical diameter which deviates from other spheres 83 by a standard deviation of  $\pm 0.01\%$  to  $\pm 30\%$ , preferably 10% or less and more preferably 1% or less. The size of the spheres 83 and flow rate of liquid 82 is controlled so that each sphere 83 contain a single particle (e.g. a single cell) to be examined. The stream of spheres 83 is caused to flow past a sensor and/or energy source of any desired type thereby allowing for a determination of precisely how much drug a patient is inhaling.

10

## EMULSIONS

In Figure 8 the liquid 75 can be a gas (e.g., air) inside a patient's respiratory system. The liquid 82 could be water or a drug which is surrounded by a second liquid 73 which is a water or surfactant. The system then forms particles 83 which have a center of one liquid and an outer coating of a different liquid.

15

## DRUG DELIVERY DEVICES

The various embodiments of components for creating aerosols described above can be used in devices for the delivery of an aerosol to a patient. The device is preferably a hand-held, self-contained device which a patient can easily carry about and use for the administration of drugs.

20

In one embodiment the pressurized canister of a device as disclosed in U.S. Patent 5,364,838 or 5,404,871 is replaced with an aerosol generating device of the type shown here in any of Figures 1, 2 or 3. The device preferably includes a means for measuring a patient's respiratory flow rate and respiratory volume. The aerosol may be generated when the patient manually actuates release of aerosol. However, the device preferably operates as the device in the 5,364,838 patent and is actuated automatically in response to a measured inspiratory flow rate and inspiratory volume. This makes it possible to repeatedly deliver aerosol to a patient at the same point in the respiratory cycle thereby improving repeatability of dosing.

25

30

In another embodiment the disposable containers and porous membranes of the device disclosed in U.S. Patent 5,544,646 is replaced with an aerosol generating device of

the type shown here in Figures 1, 2 or 3. In such an embodiment the aerosol generating device is likely to include a plurality of sources of liquid drug formulation (e.g. a plurality of feeding needles) so that a sufficient amount of formulation can be aerosolized in a sufficiently short period of time that the patient can, in a single inhalation, inhale all of the aerosol needed for a dose of the drug being delivered. An aerosol generating device of the type shown in Figure 3 is generally easier to manufacture and as such is preferred in this embodiment.

In the two embodiments described above it is preferable to create an aerosol with particles having a particle diameter in the range of about 1 to about 3 microns. This allows the particles to penetrate into the smallest channels of the lungs. However, such particles are not so small that they will not settle on the surface of these channels when inhaled - - failure to settle would cause the particles to be exhaled as with particles of smoke.

In yet another embodiment the source of aerosol of a device as disclosed in U.S. Patent 4,484,577 is replaced with an aerosol generating device of the type described here and shown in Figures 1, 2 or 3. The device of U.S. Patent 4,484,577 includes a large container into which the aerosol is dispersed. The aerosol then "hangs" in the air in the large container until it is inhaled by the patient. Using an aerosol generation device of the invention the aerosol particles can be made very small, e.g. about 1 micron or less. Particles of this size will be suspended in air in the container until inhaled. The patient can then breath normally in and out of the container until all or substantially all particles in the container have deposited themselves on the channels of the lung.

### EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention nor are they intended to represent that the experiments below are all or the only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (e.g. amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

The properties of sixteen different liquids are provided in Table 1

TABLE 1: Liquids used and some of their physical properties at 24.5°C ( $\rho$ : kg/m<sup>3</sup>,  $\mu$ : cpoise,  $\gamma$ : N/m). Also given, the symbols used in the plots.

5	Liquid	$\rho$	$\mu$	$\gamma$	Symbol
	Heptane	684	0.38	0.021	○
	Tap Water	1000	1.00	0.056	◇
	Water + glycerol 90/10 v/v	1026	1.39	0.069	△
	Water + glycerol 80/20 v/v	1052	1.98	0.068	▽
10	Isopropyl alcohol	755.5	2.18	0.021	×
	Water + glycerol 70/30 v/v	1078	2.76	0.067	○
	Water + glycerol 60/40 v/v	1104	4.37	0.067	●
	Water + glycerol 50/50 v/v	1030	6.17	0.066	○
	1-Octanol	827	7.47	0.024	◇
15	Water + glycerol 40/60 v/v	1156	12.3	0.065	△
	Water + glycerol 35/65 v/v	1167	15.9	0.064	▽
	Water + glycerol 30/70 v/v	1182	24.3	0.064	×
	Water + glycerol 25/75 v/v	1195	38.7	0.063	+
	Propylene glycol	1026	41.8	0.036	●

20

The liquids of Table 1 were forced through a feeding needle of the type shown in Figure 1. The end 5 of the feeding needle had an internal radius  $R_0$ . The exit orifice 6 had a diameter  $D$  and the wall of the pressure chamber 3 had a thickness of  $L$ . Three different devices were tested having the following dimensions: ( $D = 0.15, 0.2$ , and  $0.3$  mm;  $L = 0.1$ , 0.2 and  $0.35$  mm;  $R_0 = 0.2, 0.4$ , and  $0.6$  mm, respectively), and several distances  $H$  from the tube mouth to the orifice ranging from  $H = 0.5$  mm to  $H = 1.5$  mm have been used. The jet diameter was measured at the hole exit and was plotted as a function of the pressure difference  $\Delta P_g$  and flow rate  $Q$  respectively. Although this technique allows for jet diameters even below one micron, larger flow rates and diameters have been used in this study to diminish the measuring errors.

25

30

In order to collapse all of the data, we define a reference flow rate  $Q_o$  and diameter  $d_o$  based on the minimal values, from expressions (3) and (5), that can be attained in stable regime for a given  $\Delta P_g$ :

$$Q_o = \left( \frac{\gamma^4}{\rho_l \Delta P_g^3} \right)^{1/2}, \quad d_o = \frac{\gamma}{\Delta P_g} \quad (6)$$

where  $\gamma$  and  $\rho_l$  are the liquid-gas surface tension and the liquid density, respectively. These definitions provide the advantage of a nondimensional expression for (5), as

$$d_j/d_o = (8/\pi^2)^{1/4} (Q/Q_o)^{1/2}, \quad (7)$$

which allows for a check for the validity of neglecting the surface tension term in (4) (i.e.,  $Q/Q_o$  should be large).

Notice that if the measured  $d_j$  follows expression (5), the surface tension cancels out in (7). Also notice that  $d_j/d_o \approx We/2$ .

350 measured values of  $d_j/d_o$  versus  $Q/Q_o$  are plotted in Fig. 5. A continuous line represents the theoretical prediction (7), independent of liquid viscosity and surface tension. The use of different hole and tube diameters as well as tube-hole distances does not have any appreciable influence on  $d_j$ . The collapse of the experimental data and the agreement with the simple theoretical model is excellent. Finally, the experimental values of  $Q$  are at least four times large than  $Q_o$  (being in most cases several hundreds times larger), which justifies the neglect of the surface tension term in Eq. (4).

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

What is claimed is:

1. A device for delivery of aerosol particles to a patient comprising:  
a first means for providing a first fluid comprising a first fluid entrance  
5 port and a first fluid exit port at which the fluid is provided;  
a pressure chamber for providing a pressurized fluid to an area  
surrounding the first fluid exit port, the pressure chamber comprising a second fluid entrance  
port and a second fluid exit port.
- 10 2. The device of claim 1, wherein the first means for providing the first  
fluid is a feeding needle having a cylindrical channel therein whereby the first fluid entrance  
port and first fluid exit port are each circular;  
wherein the feeding needle exit port has a diameter in the range of from  
about 0.002 to about 2 mm, and the pressure chamber exit port has a diameter in the range of  
15 about 0.002 mm to about 2 mm.
3. The device of claim 1, wherein the first means for providing a first fluid  
is a planar channel created between a first planar member surface and a second planar  
member surface positioned parallel to the first planar member surface;  
20 wherein the first planar member is further comprised of a plurality of  
channels and the pressure chamber comprises a plurality of pressure fluid exit ports  
positioned in front of a flow path of a channel;  
wherein each channel has a diameter in the range of from about 0.01 mm  
to about 0.4 mm and the pressure chamber exit port has a diameter in the range of about 0.01  
25 mm to about 0.25 mm.
4. The device of claim 1, having inserted therein a first fluid having a  
dynamic viscosity in the range of from about  $10^{-4}$  to about 1 kg/m/sec and further wherein  
the first fluid is comprised of a pharmaceutically active drug.

30



5. A method of delivering an aerosol to a patient, comprising:  
forcing a pharmaceutically active liquid through a channel of a feeding source in a manner which causes the liquid to be expelled from an exit opening;

forcing a gas through a pressure chamber in a manner which causes the gas to exit the pressure chamber from an exit orifice in front of a flow path of the liquid expelled from the exit opening of the feeding source;

wherein a stable liquid-gas interface is maintained and the liquid forms a stable capillary jet focused on the exit orifice of the pressure chamber by the gas.

6. The method of claim 5, wherein the liquid has a viscosity in a range of from about  $0.3 \times 10^{-3}$  to about  $5 \times 10^{-2}$  kg/m/sec and the gas is air;

wherein the liquid is forced through the channel at a rate in a range of about 0.01 nl/sec to about 100  $\mu$ l/sec and further wherein the air is forced through the opening of the pressure chamber at a rate in the range of from about 50 m/sec to about 2000 m/sec;

wherein the feeding source is a cylindrical channel and the liquid is expelled from an exit opening having a diameter in the range of from about 0.002 to about 2 mm and wherein the opening in the pressure chamber has a diameter in the range of about 0.002 to about 2 mm and is positioned directly in front of a flow path of the exit opening of the channel;

wherein the exit opening in the pressure chamber has a diameter in the range of from about 0.01 mm to about 0.4 mm or more preferably 0.005 mm to about 0.25 mm; and

wherein the exit opening of the feeding source is separated by a distance of from about 0.01 to about 2 mm (or more preferably 0.002 to about 1 mm) from the exit opening in the pressure chamber.

7. A method of delivering aerosolized particles of a pharmaceutically active drug to a patient, comprising:

feeding liquid formulation comprised of a pharmaceutically active drug through a liquid feeding source to an outlet;

feeding gas through an orifice positioned in front of the outlet in a direction aligned with a direction of flow out of the outlet;

wherein the feeding of liquid and feeding of gas are each at a rate relative to each other so as to maintain a stable capillary microjet of liquid which exits the orifice and forms aerosolized particles having a size in the range of about 0.1 micron to about 10 microns.

8. The method of claim 7, wherein gas is forced into an area around the feeding source outlet at a pressure in the range of 10 to 50,000 mBar above atmospheric pressure and further wherein the liquid has a viscosity in the range of from  $10^{-4}$  to 1 kg/m/sec;

wherein gas from the pressure chamber surrounds liquid exiting the feeding source outlet which liquid is drawn into the orifice concentrically being focused by the gas flowing out of the outlet, and further wherein the aerosolized particles formed are uniform in size to the extent of having a relative size standard deviation of 1% to 30%.

9. A monodisperse aerosol of particles of a pharmaceutically active drug, the particles characterized by having the same diameter with a deviation in diameter from one particle to another in a range of from about  $\pm 3\%$  to  $\pm 30\%$ .

10. The monodisperse aerosol of claim 9, wherein the particles are comprised of a liquid formulation of the drug and a carrier and wherein the particles have a size in a range of from about 1 micron to about 5 microns and the particles have a standard size deviation of less than  $\pm 5\%$ .

11. The monodisperse aerosol of claim 10, wherein the particles are comprised of a dry powder of drug and wherein the particles have a size in a range of from about 1 micron to about 5 microns and the particles have a standard size deviation of less than  $\pm 5\%$ .

12. A monodisperse aerosol of hollow droplets comprised of a carrier and a pharmaceutically active drug, wherein the hollow droplets have air in their center and have an actual physical size diameter in a range of from about 200 microns to 1 micron.

5 13. The monodisperse aerosol of claim 12, wherein the diameter is in a range of from about 50 microns to 1 micron and the hollow droplets have a standard size deviation in diameter from one particle to another in a range of from about  $\pm 0.01\%$  to  $\pm 30\%$ .

10 14. The monodispersion of claim 13, wherein the diameter is in a range of from about 10 microns to about 1 micron and each hollow droplet is substantially identical to other hollow droplets in size with a deviation of less than 1%.

1/6

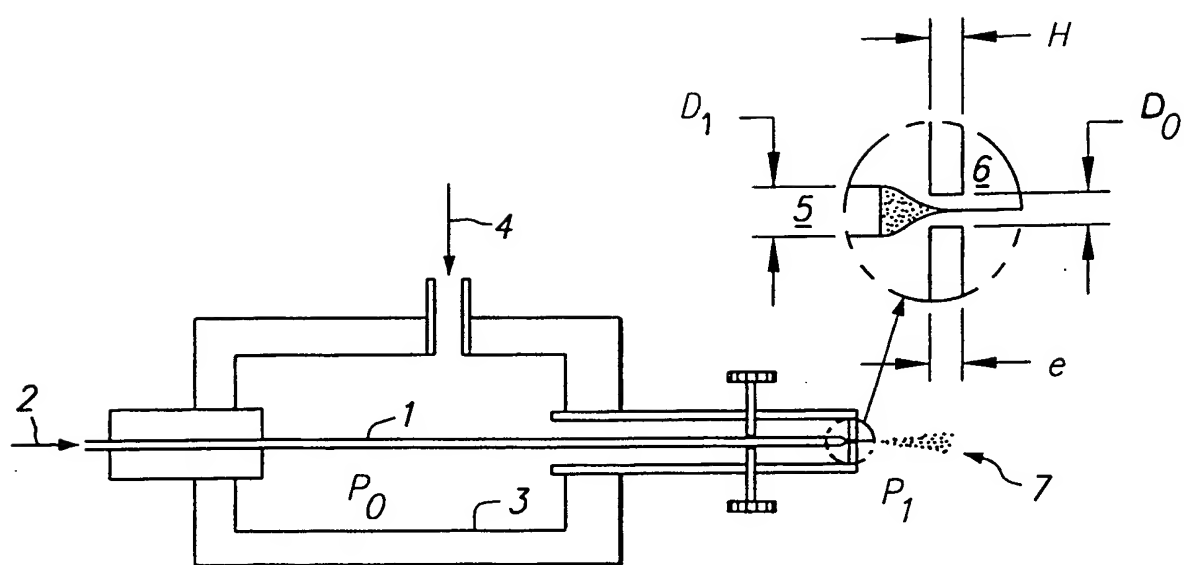


FIG. 1

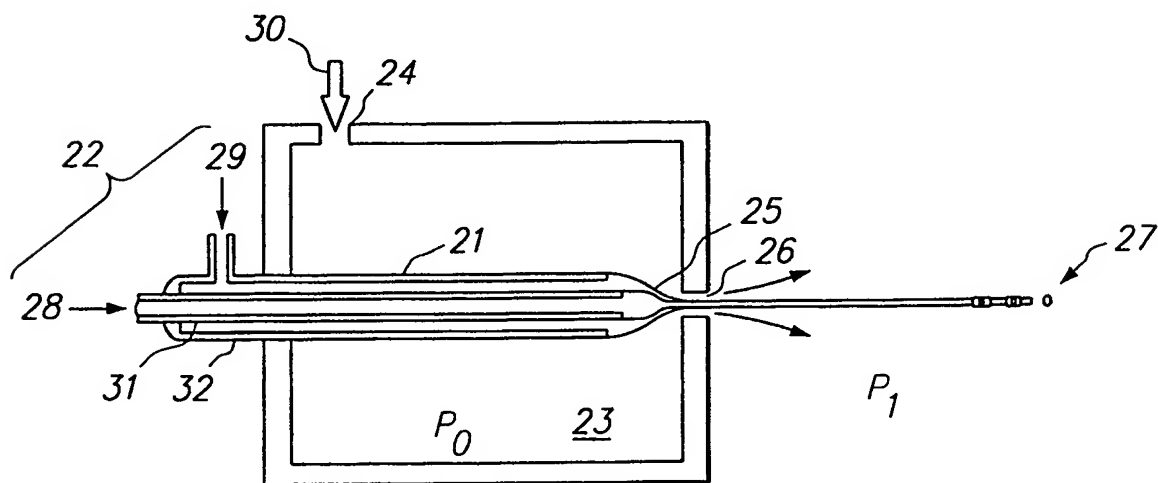


FIG. 2

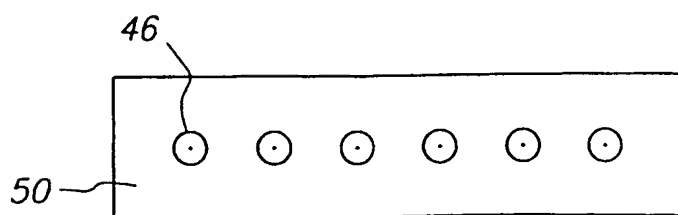
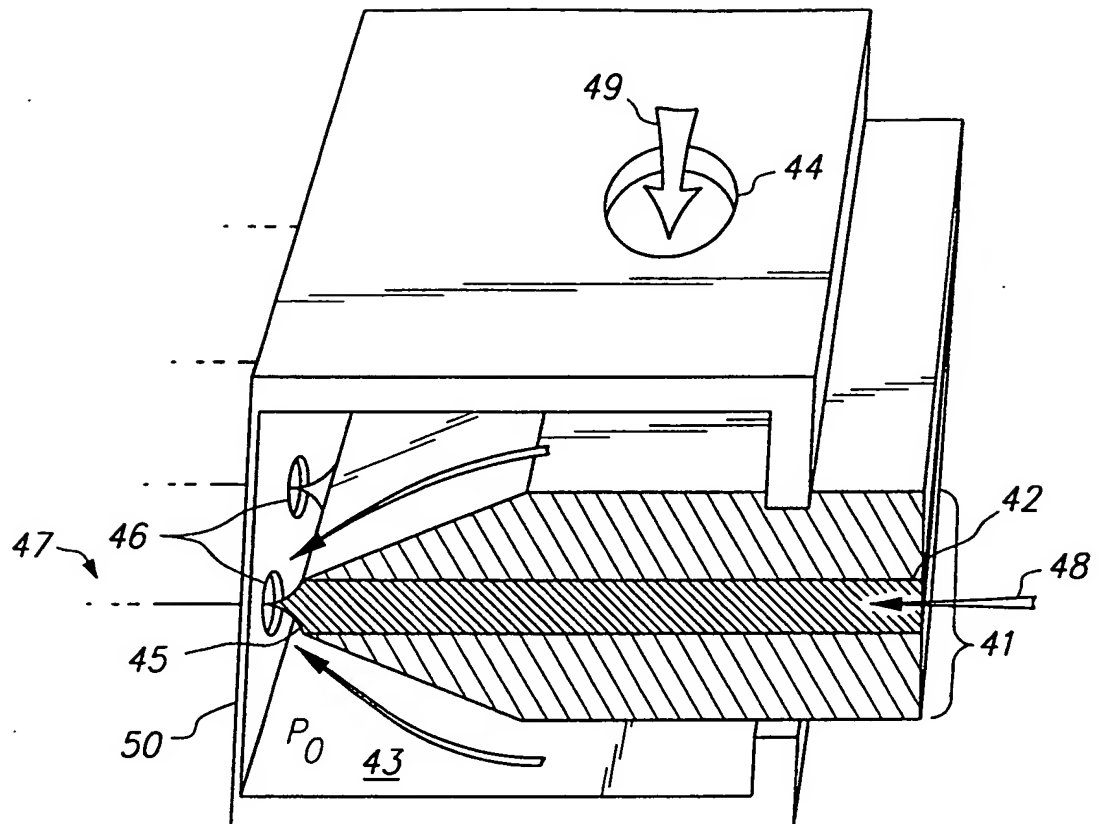
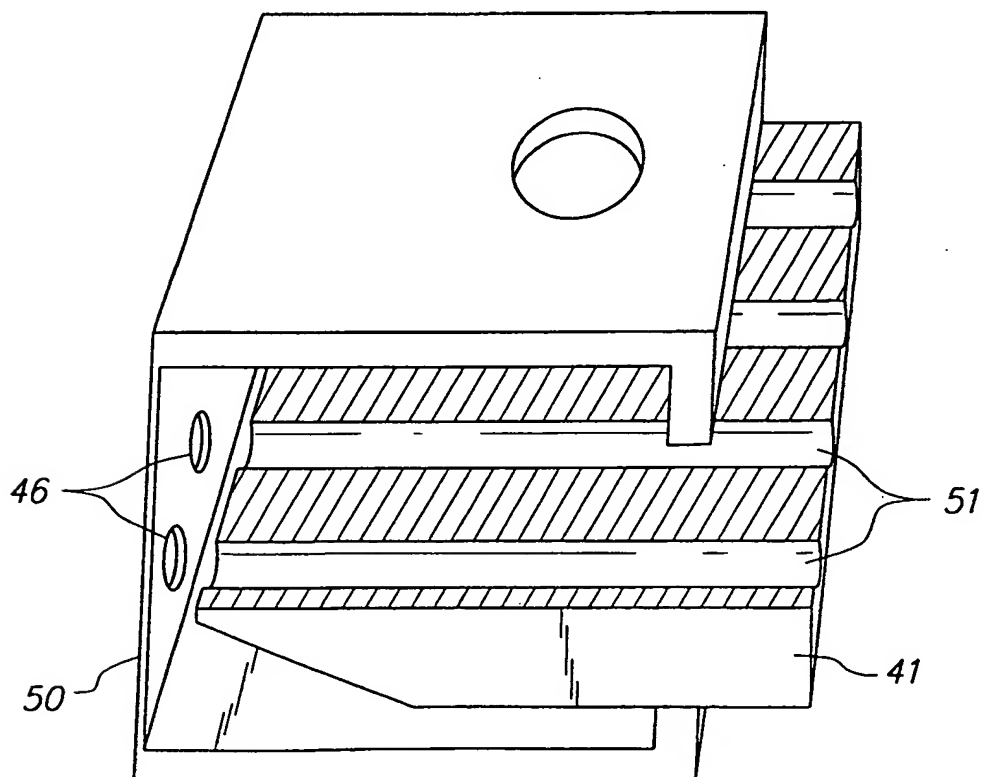
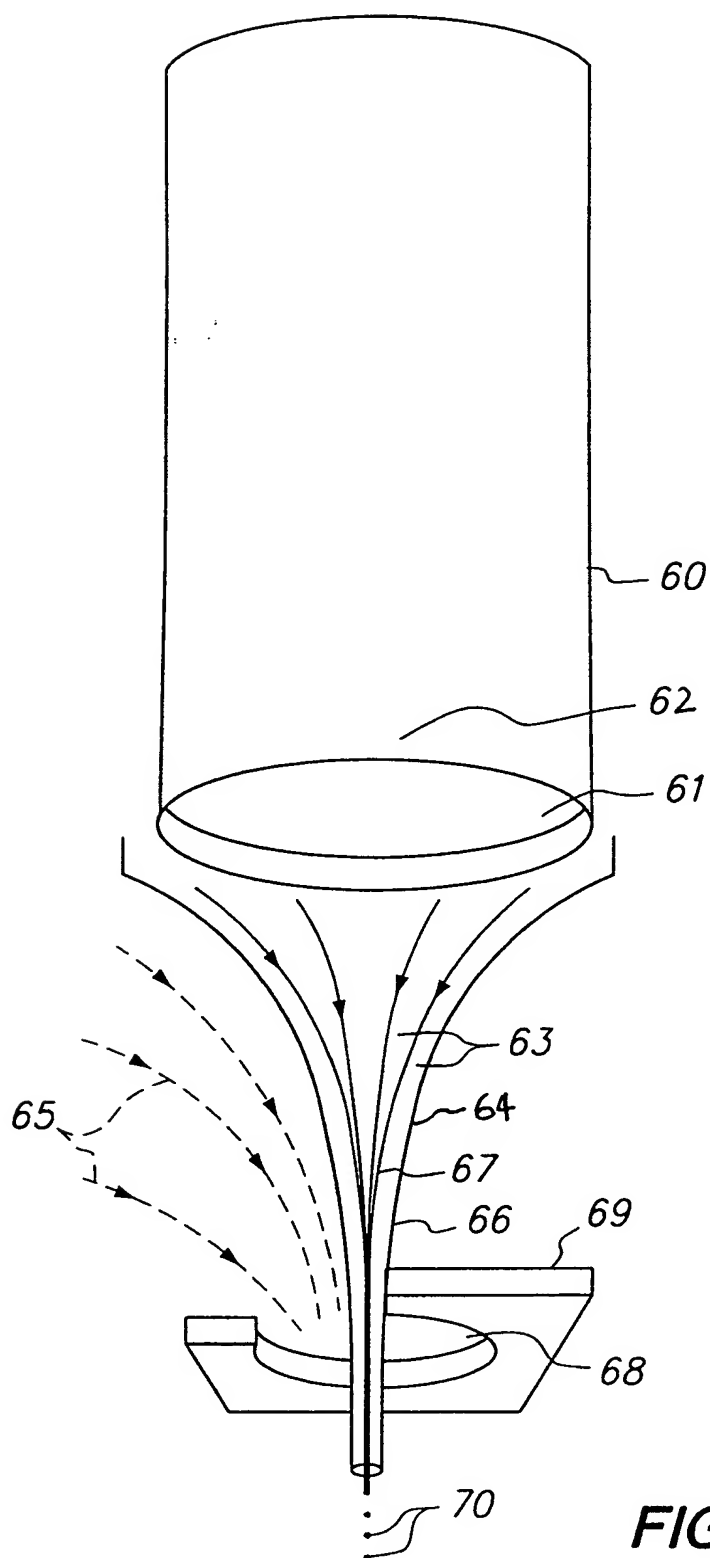


FIG. 3B

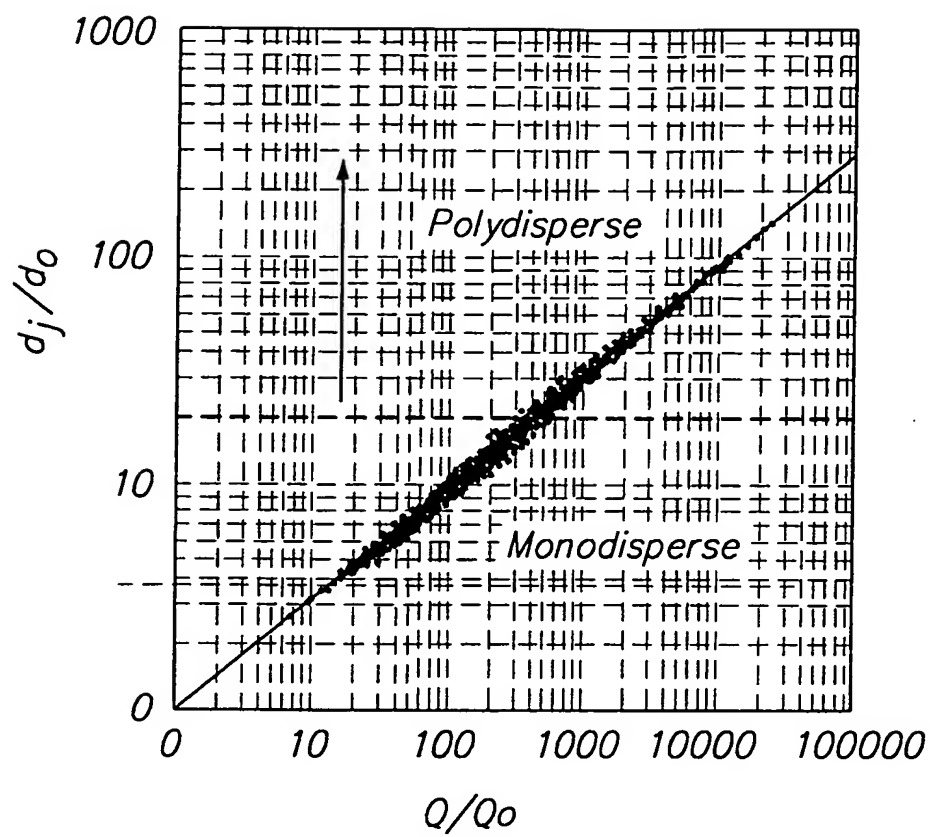
2/6

**FIG. 3A****FIG. 3C**

3/6

**FIG. 4**

4/6

**FIG. 5**

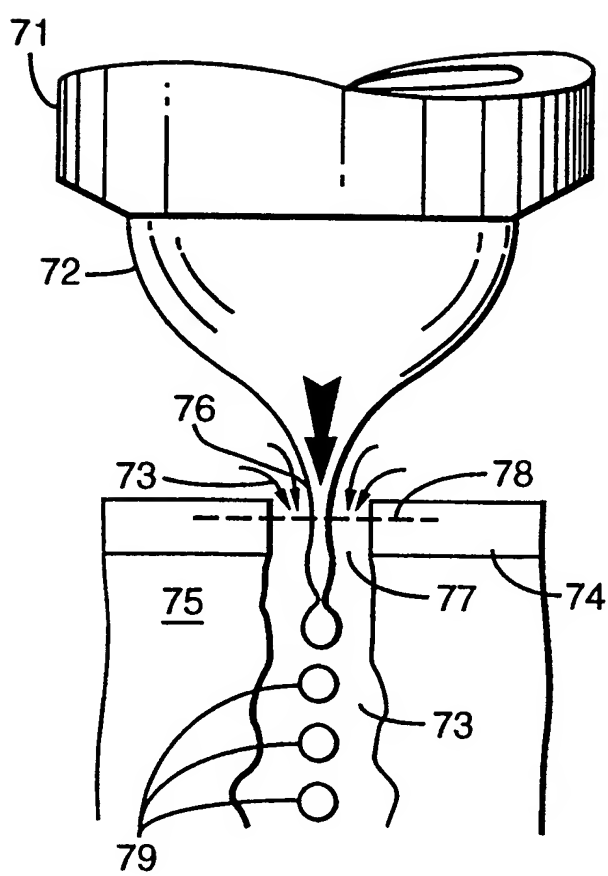


FIG. 6

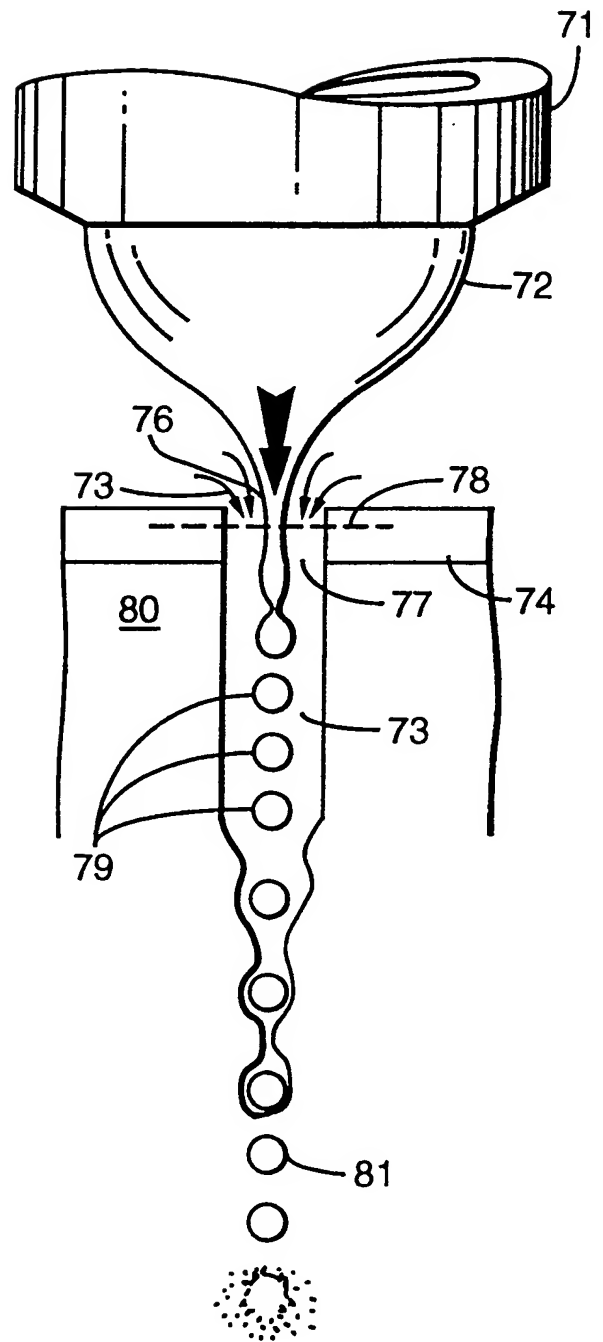


FIG. 7



6/6

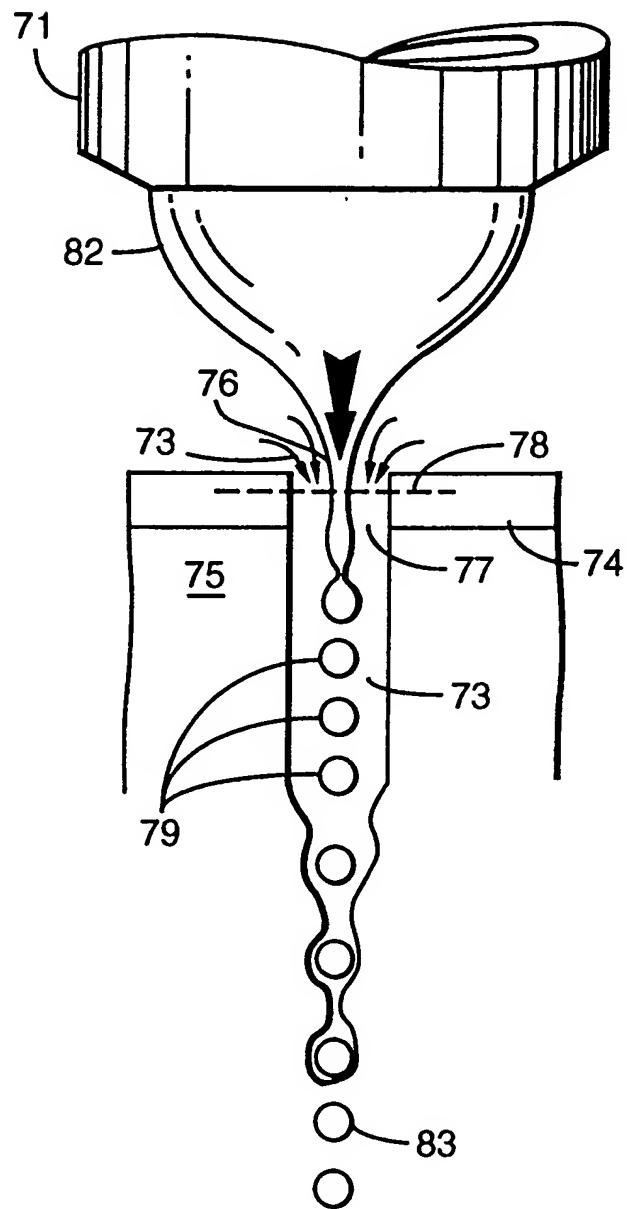


FIG. 8

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 B05B7/06 A61M15/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 B05B A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 43048 A (GANAN CALVO ALFONSO ;UNIV SEVILLA (ES); BARRERO RIPOLL ANTONIO (ES) 20 November 1997	1,2,4,9
A	see page 4, line 12 - page 5, line 6 see page 6, line 4 - line 6 see page 6, line 18 - line 22 see page 7, line 4 - line 24 see page 9, line 23 - line 27 see page 10, line 8 - page 11, line 12; claims 2-13; figure ---	10
X	US 3 700 170 A (BLANKA DOHNALOVA-BINKOVA ET AL) 24 October 1972 see column 3, line 28 - line 45 see column 5, line 6 - line 30 --- -/--	9-11

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*Z\* document member of the same patent family

Date of the actual completion of the international search

24 March 1999

Date of mailing of the international search report

26. 04. 1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Brévier, F

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 44080 A (GLAXO GROUP LTD ;OORT MICHIEL MARY VAN (US); SACCHETTI MARK JOSEPH) 27 November 1997 see page 11, line 29 - page 14, line 22; figure 2 ---	1,2
A	WO 91 18682 A (WEYERHAEUSER CO) 12 December 1991 see page 11, line 14 - page 12, line 21 see page 13, line 13 - line 29 see page 50, line 34 - page 51, line 12; figures 3-8,43 ---	3
A	WO 94 11116 A (SUNDHOLM PATRICK ;DONNELLY ROBERT (NZ); KANGAS MARTTI (US)) 26 May 1994 see page 4, line 29 - line 37; figures 1,4 ---	3
A	US 5 235 969 A (BELLM HOWARD G) 17 August 1993 see column 1, line 34 - line 43 see column 10, line 23 - line 43 see column 11, line 34 - line 41; figure 19 ---	9,10
A	WILLIAM C. HINDS: "Aerosol technology. Properties, behavior, and measurement of airborne particules" 1982 , JOHN WILEY & SONS , U.S.A. XP002096608 cited in the application see page 379 - page 383 ---	11
A	WO 95 23030 A (FLOW RESEARCH EVALUATION DIAGN ;THOMAS NEALE (GB)) 31 August 1995 see page 8, line 20 - line 27; figure 9 -----	12

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 5-8  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
Rule 39.1 (IV) Pct, Method for treatment of the human or animal body by therapy
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

T/IB 98/02055

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9743048	A	20-11-1997	NONE	
US 3700170	A	24-10-1972	CS 153231 B DE 2132389 A	25-02-1974 08-06-1972
WO 9744080	A	27-11-1997	AU 2958897 A EP 0900101 A	09-12-1997 10-03-1999
WO 9118682	A	12-12-1991	US 5332458 A AU 8072491 A CA 2084185 A EP 0532659 A FI 925404 A AU 9132791 A CA 2101264 A EP 0569378 A FI 933323 A JP 6504479 T WO 9212803 A CA 2102102 A EP 0605475 A JP 6507130 T MX 9201659 A WO 9219449 A US 5292391 A	26-07-1994 31-12-1991 01-12-1991 24-03-1993 27-11-1992 27-08-1992 25-07-1992 18-11-1993 23-07-1993 26-05-1994 06-08-1992 30-10-1992 13-07-1994 11-08-1994 01-07-1993 12-11-1992 08-03-1994
WO 9411116	A	26-05-1994	FI 925045 A FI 934890 A,B, AU 5421794 A CA 2148505 A DE 69323438 D EP 0682571 A	07-05-1994 07-05-1994 08-06-1994 26-05-1994 18-03-1999 22-11-1994
US 5235969	A	17-08-1993	AT 140157 T AU 1236792 A DE 69212143 D DE 69212143 T EP 0573457 A WO 9215354 A	15-07-1996 06-10-1992 14-08-1996 07-11-1996 15-12-1993 17-09-1992
WO 9523030	A	31-08-1995	AU 1816595 A EP 0835163 A JP 9509363 T US 5810260 A	11-09-1995 15-04-1998 22-09-1997 22-09-1998

**THIS PAGE BLANK (USPTO)**